

## 2-(Alkylamino)nicotinic Acid and Analogs. Potent Angiotensin II Antagonists<sup>1</sup>

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A series of pyridines and other six-membered ring heterocycles connected to a biphenyltetrazole with a  $-\text{CH}_2-\text{NR}'$ -link (1) were discovered to be potent angiotensin II antagonists. In the pyrimidine carboxylic acid series ( $\text{W} = \text{CR}$ ,  $\text{X} = \text{N}$ ,  $\text{Y} = \text{CH}$ ,  $\text{Z} = \text{COOH}$ ), compounds with an alkyl group ( $\text{R}'$ ) on the exocyclic nitrogen were much more potent than compounds with an alkyl group ( $\text{R}$ ) on the heterocyclic ring. The corresponding pyridine, pyridazine, pyrazine, and 1,2,4-triazine carboxylic acids also showed potent in vitro angiotensin II antagonism. The pyridine ( $\text{W}$ ,  $\text{X}$ ,  $\text{Y} = \text{CH}$ ,  $\text{Z} = \text{COOH}$ ,  $\text{R}' = n\text{-C}_3\text{H}_7$ ) demonstrated potent in vitro activity ( $\text{pA}_2 = 10.10$ , rabbit aorta, and  $\text{K}_i = 0.61 \text{ nM}$ , receptor binding in rat liver) as well as exceptional oral antihypertensive activity and bioavailability. Any nonacidic replacement for the carboxylic acid was detrimental for activity.

The renin-angiotensin system (RAS) is known to play an important role in cardiovascular regulation. On the basis of the success of the angiotensin-converting enzyme inhibitors as antihypertensive drugs, there has been intense effort in the pharmaceutical industry to discover renin inhibitors and angiotensin II (A-II) antagonists as alternative means of inhibiting the RAS. The development of nonpeptide A-II antagonists was initiated by Takeda chemists, who reported on imidazoles such as 2a, which possessed weak activity.<sup>2</sup> DuPont scientists subsequently discovered the importance of linking the imidazole to a biphenyltetrazole moiety, leading to the discovery of the orally active DUP-753 (Losartan 2b),<sup>3</sup> which is in clinical trials.

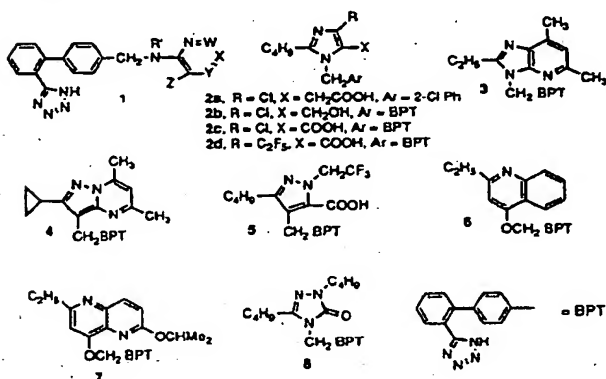
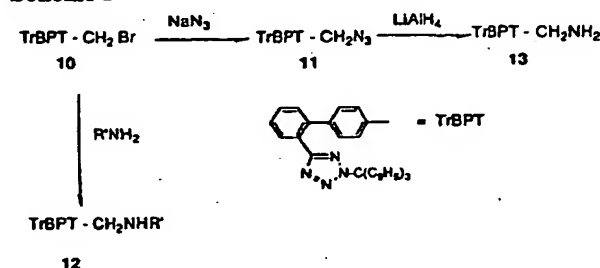


Figure 1.

Since then, there have been many other reports of A-II antagonists that contain an alkyl-substituted nitrogen heterocycle connected to a biphenyltetrazole by a methylene or an ether link. Examples of these heterocycles include imidazo[4,5-b]pyridine (3),<sup>4</sup> pyrazolo[1,5-a]pyrimidine (4),<sup>5</sup> pyrazole (5),<sup>6,7</sup> quinoline (6),<sup>8</sup> 1,5-naphthyridine (7),<sup>9</sup> and triazolones (8).<sup>10</sup>

At the start of our work, only the imidazole-containing A-II antagonists 2a-d were known. We chose to examine

### Scheme I



related compounds based on six membered ring heterocycles. From the published structures, it appeared that a target compound should incorporate a carboxylic acid, an alkyl group, and a tetrazole-substituted biphenyl moiety, each attached to the central heterocycle. What remained to be determined, however, was the exact placement of these groups on a six membered ring, and the optimum choice for the heterocycle itself.

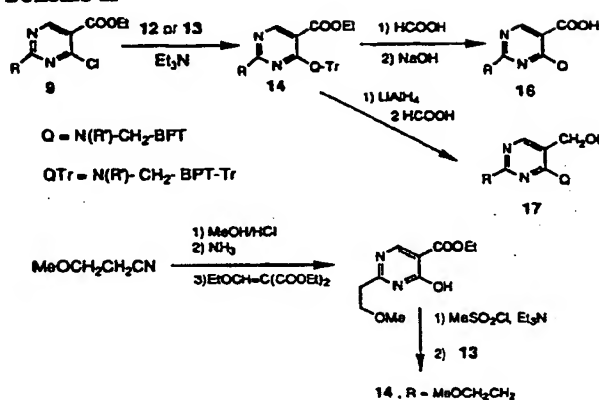
Heterocycles that incorporated a number of these features, such as pyrimidines 9<sup>11</sup> (Scheme II) and pyridines 29 (Scheme VI), were readily synthesized. Furthermore, they contained a reactive chlorine through which the biphenyltetrazole group could be easily attached via a heteroatom linkage. A nitrogen was chosen for this purpose since an amine was sufficiently reactive to add to the activated heterocycles and the nitrogen would also provide a region for additional structure exploration.

### Chemistry

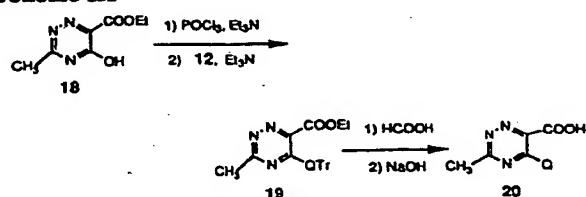
The chloropyrimidines 9<sup>11</sup> were directly coupled (see Scheme II) with amino derivatives of the biphenyltetrazole (12 and 13). These were prepared from the known (bromomethyl)biphenyltetrazole<sup>12</sup> (see Scheme I). The trityl-protected compounds (14) were deprotected under acidic conditions to give the esters, which were then hydrolyzed with base to the carboxylic acids 16. Alcohols 17 were obtained by reduction of 14 with  $\text{LiAlH}_4$  followed by detritylation with acid. When  $\text{R} = \text{CH}_3\text{OCH}_2\text{CH}_2$ , 9 could not be prepared from the corresponding hydroxyl compound without cleaving the ether. Instead the product

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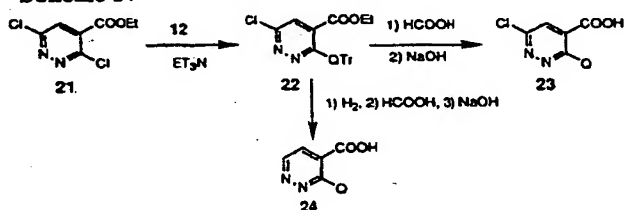
## Scheme II



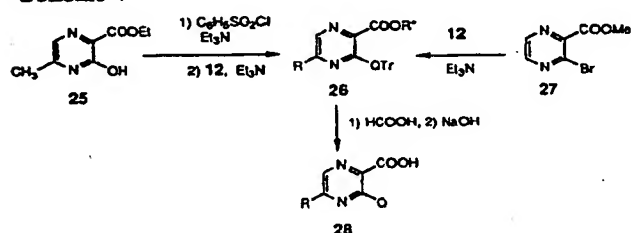
## Scheme III



## Scheme IV



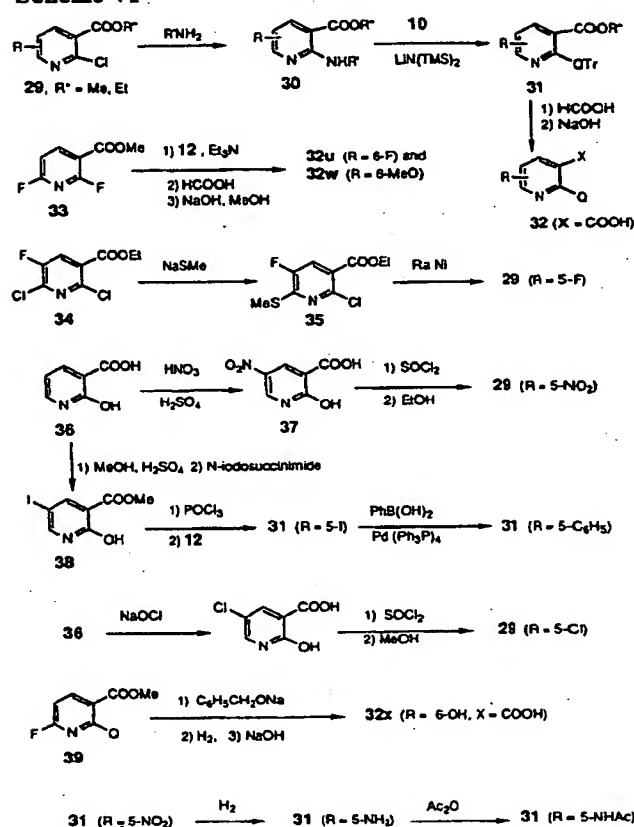
## Scheme V



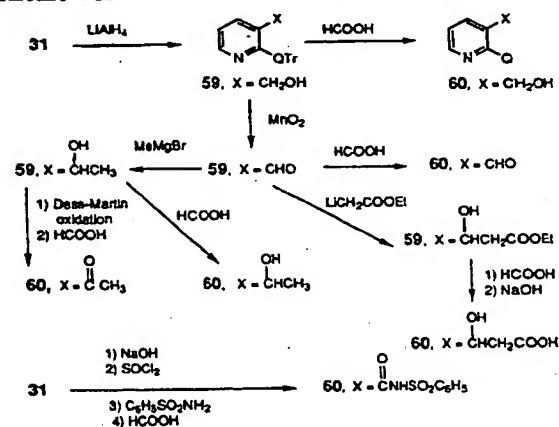
was made by way of the methanesulfonate intermediate (see Scheme II). Similarly, 1,2,4-triazines, pyrazines, and pyridazines were prepared from esters 18, 21, and 25, respectively, using halogen or benzenesulfonate leaving groups (see Schemes III-V).

The chloronicotinic acids 29 (R = H, Me, and Cl) did not react with the secondary amine 12. Therefore these pyridines were constructed in two steps (Scheme VI). Reaction of primary amines with 29 yielded 2-(alkylamino)nicotinic acids 30, which were alkylated with bromide 10 to give the protected compounds 31. When R = 6-F, 5-F, or 5-I, the 2-chloro group in 29 could be directly displaced with the secondary amine 12. Ethyl 2,6-difluoronicotinate<sup>14</sup> reacted with 12 in the desired 2-position, based on the diagnostic splitting observed between the 6-F and 5-H in the <sup>1</sup>H NMR spectrum. The 5-fluoro compound was prepared from the known<sup>15</sup> compound 34, by displacement with methyl mercaptan in the 6-position (structure de-

## Scheme VI



## Scheme VII

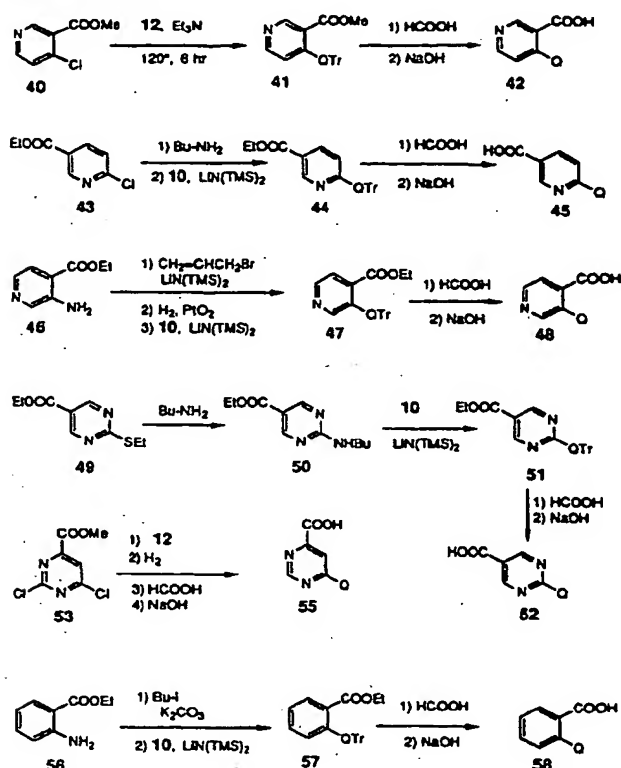


termination by X-ray) and subsequent desulfurization of 35 with Raney nickel to give 29 (R = 5-F).

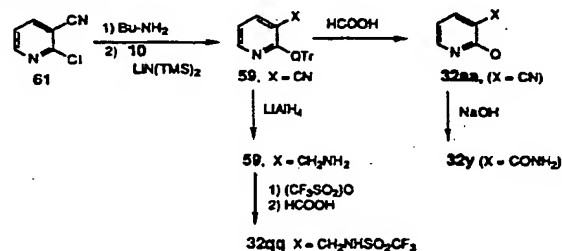
The other substituents (Cl, I, NO<sub>2</sub>) at the 5-position of the nicotinic acid were introduced by way of electrophilic substitution on 36 (see scheme VI). The 5-phenyl analog was conveniently made by a palladium-catalyzed coupling reaction of the 5-iodo ester 31 with phenyl boronic acid. The 6-hydroxy compound was prepared from the 6-fluoro compound as shown.

The 5-carboxy group in 31 was converted to CH<sub>2</sub>OH, CHO, CH(OH)Me, CH(OH)CH<sub>2</sub>COOH, COCH<sub>3</sub>, and CONHSO<sub>2</sub>C<sub>6</sub>H<sub>5</sub> groups as outlined in Scheme VII. The starting material for the synthesis of the 3-CN, CONH<sub>2</sub>, and CH<sub>2</sub>NHSO<sub>2</sub>CF<sub>3</sub> analogs was 2-chloronicotinitrile

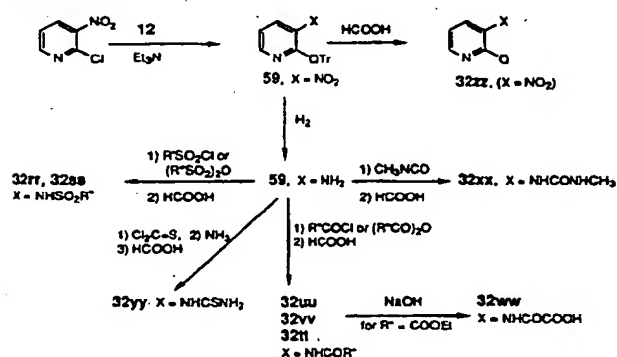
## Scheme VIII



## Scheme IX

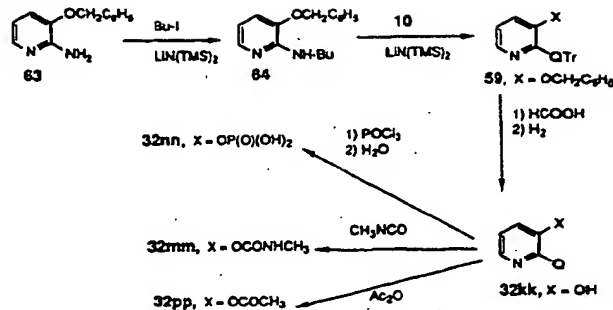


## Scheme X

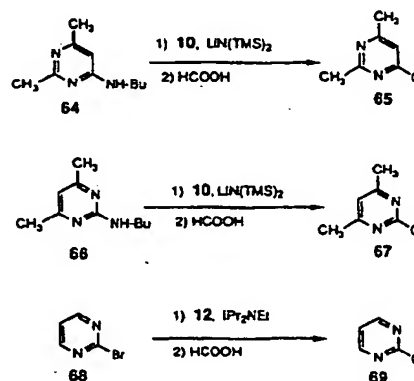


(Scheme IX). 3-Nitro-2-chloropyridine reacted with 12 to yield the nitro compound 59, which was converted into a wide variety of 3 nitrogen-substituted nicotinic acid analogs as shown in Scheme X. Commercially available 2-amino-3-(benzyloxy)pyridine (63) was transformed into several 3-oxygen-substituted analogs as shown in Scheme XI.

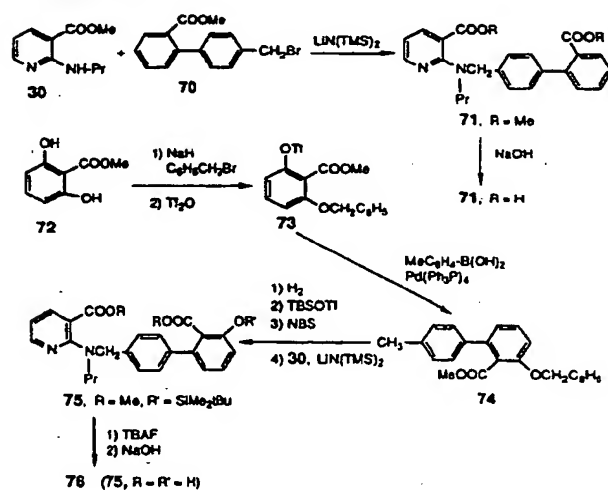
## Scheme XI



## Scheme XII

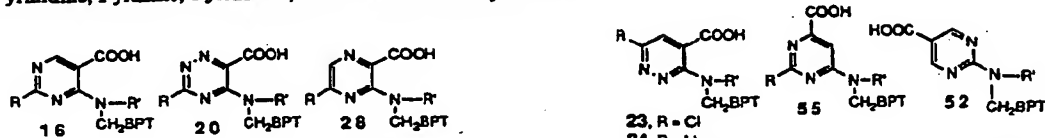


## Scheme XIII



All of the above compounds possessed a common alkylamino linking group which was flanked on one side by a carboxyl or other polar group, and on the other side by a ring nitrogen. To study the effect of varying the position of the ring nitrogen and carboxylic acid relative to the linking group, other pyridines and pyrimidines were synthesized (Scheme VIII). The methods used were as follows: (1) direct secondary amine 12 displacement of a halo heterocycle (i.e. 40 and 53); (2) sequential displacement and alkylation (i.e. 43 and 49); and (3) double alkylation of a heterocyclic primary amine (46 and 56). The simple methyl and unsubstituted pyrimidine analogs were synthesized from the known starting materials 64, 66, and 68 (Scheme XII).

Table I. Pyrimidine, Pyrazine, Pyridazine, and Triazine Carboxylic Acids



no.	R	R'	pA <sub>2</sub> <sup>a</sup>	mp <sup>b</sup> (°C)	formula <sup>c</sup>
16a	H	H	5.61 (0.08) 2	a	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> ·0.65C <sub>2</sub> H <sub>5</sub> OH
16b	CH <sub>3</sub>	H	7.50 (0.11) 2	211-212	C <sub>11</sub> H <sub>11</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·H <sub>2</sub> O
16c	C <sub>2</sub> H <sub>5</sub>	H	8.30 (0.04) 2	200-202	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.5H <sub>2</sub> O
16d	C <sub>3</sub> H <sub>7</sub>	H	8.27 (0.37) 2	223-225	C <sub>13</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> ·HCl
16e	C <sub>4</sub> H <sub>9</sub>	H	7.91 (0.23) F	193-195	C <sub>14</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.33H <sub>2</sub> O
16f	C <sub>5</sub> H <sub>11</sub>	H	7.23 (0.07) 2	166-168	C <sub>15</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·H <sub>2</sub> O
16g	CH <sub>3</sub> OCH <sub>2</sub> CH <sub>3</sub>	H	6.81 (0.01) 2	235	C <sub>12</sub> H <sub>13</sub> N <sub>2</sub> O <sub>5</sub> ·0.5H <sub>2</sub> O
16h	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	7.15 (0.02) 2	165-169	C <sub>14</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·H <sub>2</sub> O
16i	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	7.96 (0.02) 2	a	C <sub>12</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> ·0.70H <sub>2</sub> O
16j	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	9.60 (0.19) F	a	C <sub>13</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub> ·0.75H <sub>2</sub> O
16k	CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	8.81 (0.16) F <sup>†</sup>	155-158	C <sub>14</sub> H <sub>17</sub> N <sub>2</sub> O <sub>3</sub> ·HCl·0.5H <sub>2</sub> O
16l	CH <sub>3</sub>	C <sub>5</sub> H <sub>11</sub>	8.73 (0.05) 2	a	C <sub>15</sub> H <sub>19</sub> N <sub>2</sub> O <sub>3</sub> ·0.75H <sub>2</sub> O <sup>d</sup>
16m	CH <sub>3</sub>	CH <sub>2</sub> CH=CH <sub>2</sub>	8.32 (0.14) F	a	C <sub>13</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> ·0.5HCl <sup>d</sup>
16n	CH <sub>3</sub>	CH <sub>2</sub> CHMe <sub>2</sub>	7.50 (0.04) 2	a	C <sub>14</sub> H <sub>17</sub> N <sub>2</sub> O <sub>3</sub> ·0.5HCl <sup>d</sup>
16o	CH <sub>3</sub>	(CH <sub>2</sub> ) <sub>2</sub> CHMe <sub>2</sub>	8.85 (0.03) 2	a	C <sub>15</sub> H <sub>19</sub> N <sub>2</sub> O <sub>3</sub> ·0.5HCl
16p	CH <sub>3</sub>	CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	8.50 (0.01) 2	a	C <sub>13</sub> H <sub>15</sub> N <sub>2</sub> O <sub>5</sub> ·0.75H <sub>2</sub> O
16q	H	C <sub>3</sub> H <sub>7</sub>	9.68 (0.09) F	a	C <sub>12</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub> ·0.75H <sub>2</sub> O
16r	H	C <sub>4</sub> H <sub>9</sub>	9.57 (0.16) F	a	C <sub>13</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub> ·HCl <sup>†</sup>
16s	C <sub>2</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	8.52 (0.04) 2	a	C <sub>13</sub> H <sub>15</sub> N <sub>2</sub> O <sub>3</sub> ·0.75H <sub>2</sub> O
16t	CF <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	8.79 (0.09) 2	a	C <sub>12</sub> H <sub>9</sub> F <sub>3</sub> N <sub>2</sub> O <sub>3</sub> ·0.1H <sub>2</sub> O
16u	CH <sub>3</sub> S	C <sub>4</sub> H <sub>9</sub>	8.38 (0.11) 2	a	C <sub>14</sub> H <sub>17</sub> N <sub>2</sub> O <sub>3</sub> ·S·HCl·0.5H <sub>2</sub> O
55	H	C <sub>4</sub> H <sub>9</sub>	7.95 (0.06) 2	a	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ·0.25H <sub>2</sub> O
52	H	C <sub>4</sub> H <sub>9</sub>	8.48 (0.04) 2	a	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>3</sub> ·0.25H <sub>2</sub> O·0.1i-PrOH
20	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	8.00 (0.07) F	a	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>
28a	CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	8.90 (0.03) 3	102-104	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·Et <sub>2</sub> O
28b	H	C <sub>4</sub> H <sub>9</sub>	9.70 (0.10) 6	a	C <sub>13</sub> H <sub>13</sub> N <sub>2</sub> O <sub>3</sub>
23a	Cl	C <sub>3</sub> H <sub>7</sub>	8.31 (0.08) 2	a	C <sub>12</sub> H <sub>10</sub> ClN <sub>2</sub> O <sub>3</sub> ·0.25i-PrOH
23b	Cl	C <sub>4</sub> H <sub>9</sub>	9.04 (0.12) 2	a	C <sub>13</sub> H <sub>11</sub> ClN <sub>2</sub> O <sub>3</sub> ·0.25i-PrOH
24a	H	C <sub>3</sub> H <sub>7</sub>	9.69 (0.20) 6	a	C <sub>12</sub> H <sub>11</sub> N <sub>2</sub> O <sub>3</sub> ·0.25i-PrOH
24b	H	C <sub>4</sub> H <sub>9</sub>	10.25 (0.15) 4	a	C <sub>13</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> ·0.5H <sub>2</sub> O

<sup>a</sup> pA<sub>2</sub> in rabbit aorta (standard error), no. of determinations for estimated pA<sub>2</sub>, or F for full pA<sub>2</sub>. Slope for full pA<sub>2</sub> is between 0.95 and 1.15 unless otherwise noted. See Experimental Section. <sup>b</sup> "a" denotes amorphous or no attempt was made to crystallize the compound. <sup>c</sup> Analysis for C, H, and N are within ±0.4% of theory. <sup>d</sup> Nitrogen low by 0.4 to 1.0%. <sup>e</sup> C: calcd, 59.29; found, 60.07. <sup>f</sup> H: calcd, 5.15; found, 5.68. <sup>†</sup> Slope = 1.21.

The benzoic and salicylic acid analogs of the phenyltetrazole were synthesized as outlined in Scheme XIII. Starting material 70<sup>12</sup> was used in place of 10 to prepare the carboxylic acid 71. The salicylic acid was synthesized by a palladium coupling of triflate 73 with tolyl boronic acid to give biphenyl 74 which was ultimately converted to the desired compound 76.

## Biology

**Antagonism of Angiotensin II in the Rabbit Aorta.** The compounds were evaluated for their potency in antagonizing the ability of angiotensin II to contract the rabbit aorta. Potencies were calculated as pA<sub>2</sub> values, the definition of which is as follows. If at drug concentration of 10<sup>-x</sup> molar in the bath, one must double the concentration of angiotensin II to get the same effect on the rabbit aorta that one gets without the drug, then the pA<sub>2</sub> is x. The higher the pA<sub>2</sub> value, the more potent the drug. The standard error in the pA<sub>2</sub> determination varies, but we would consider a pA<sub>2</sub> difference of 0.25 between two compounds to be meaningful. See the Experimental Section for the difference between a full and estimated pA<sub>2</sub>, and for the definition of the slope.

Our first series of compounds were the CH<sub>2</sub>NH linked 2-alkyl pyrimidine carboxylic acids (Table I, compounds 16a-g). The 2-ethyl and 2-propyl compounds had pA<sub>2</sub> values of 8.27 and 8.30, respectively, in the rabbit aorta, and thus were comparable in vitro to DUP-753. Shorter

or longer alkyl groups weakened activity. The corresponding esters and alcohols (Table II) were roughly 3-fold weaker.

Conversion of the secondary amine in the linking group to a tertiary amine improved in vitro potency. Highly potent A-II antagonists were achieved with the *n*-propyl 16q and *n*-butyl 16r derivatives. The optimal substituent in the 2-position was hydrogen. Pyrimidine isomers (52 and 55) were much less potent.

The methyltriazine 20 was less active than the corresponding pyrimidine 16j, while the pyrazine 28b and pyridazine 24b were equal or slightly more active than the corresponding pyrimidine 16k. A chlorine on the pyridazine ring (23) reduced potency.

Removing one of the nitrogens in the pyrimidine ring resulted in the pyridine series which proved to be 5-fold more potent (compare 32c, Table III to 16q, Table I). The optimal substituent on the exocyclic nitrogen was either *n*-propyl or *n*-butyl. Any substitution on the pyridine ring (Table IV) reduced the activity; the most detrimental being 6-MeO or 6-OH; the least detrimental being 4-CH<sub>3</sub>, 5- or 6-F, and 5-Cl. The 5-position could tolerate a degree of bulk, e.g. phenyl, but polar groups, e.g. AcNH or NH<sub>2</sub> were not accommodated. Compound 32f with a pA<sub>2</sub> of 10.33 and 32c (A-81988) with a pA<sub>2</sub> of 10.10 are among the best angiotensin II antagonists described to date (see Table VII). A-81988, 16q, and 16r showed competitive antagonism (slopes = 1.06-1.09) whereas L158809 (3, slope = 1.37), DUP-532 (2d, slope = 1.81), EXP-3174 (2c, slope =

Table II. SAR of 2-Alkylpyrimidines—Noncarboxylic Acids

no.	R	X	pA <sub>2</sub> <sup>a</sup>	mp <sup>b</sup> (°C)	formula <sup>c</sup>
15a	H	COOEt	6.24 (0.08) 2	a	C <sub>11</sub> H <sub>13</sub> N <sub>7</sub> O <sub>2</sub>
15b	CH <sub>3</sub>	COOEt	7.13 (0.07) 2	121–123	C <sub>12</sub> H <sub>15</sub> N <sub>7</sub> O <sub>2</sub>
15c	C <sub>2</sub> H <sub>5</sub>	COOEt	7.78 (0.05) 4	114–116	C <sub>13</sub> H <sub>17</sub> N <sub>7</sub> O <sub>2</sub>
15d	C <sub>3</sub> H <sub>7</sub>	COOEt	7.91 (0.02) 2	132–133	C <sub>14</sub> H <sub>19</sub> N <sub>7</sub> O <sub>2</sub>
15e	C <sub>4</sub> H <sub>9</sub>	COOEt	7.37 (0.02) 2	145–146	C <sub>15</sub> H <sub>21</sub> N <sub>7</sub> O <sub>2</sub>
15f	C <sub>5</sub> H <sub>11</sub>	COOEt	6.37 (0.32) 2	131–133	C <sub>16</sub> H <sub>23</sub> N <sub>7</sub> O <sub>2</sub>
15g	CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	COOEt	7.10 (0.03) 2	122–124	C <sub>14</sub> H <sub>19</sub> N <sub>7</sub> O <sub>4</sub> <sup>d</sup>
17b	CH <sub>3</sub>	CH <sub>2</sub> OH	7.12 (0.06) 2	199–201	C <sub>12</sub> H <sub>15</sub> N <sub>7</sub> O <sub>2</sub> <sup>d</sup>
17c	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OH	7.96 (0.02) 2	217–219	C <sub>13</sub> H <sub>17</sub> N <sub>7</sub> O <sub>2</sub> <sup>d</sup>
17d	C <sub>3</sub> H <sub>7</sub>	CH <sub>2</sub> OH	7.60 (0.44) F	214–216	C <sub>14</sub> H <sub>19</sub> N <sub>7</sub> O <sub>2</sub> <sup>d</sup>
17e	C <sub>4</sub> H <sub>9</sub>	CH <sub>2</sub> OH	7.53 (0.21) F	152–159	C <sub>15</sub> H <sub>21</sub> N <sub>7</sub> O <sub>2</sub> <sup>d</sup>
17g	CH <sub>2</sub> OCH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> OH	6.41 (0.11) 2	218–220	C <sub>14</sub> H <sub>19</sub> N <sub>7</sub> O <sub>4</sub> <sup>d</sup>
65			7.90 (0.06) 3	a	C <sub>12</sub> H <sub>15</sub> N <sub>7</sub> <sup>d</sup>
67			7.65 (0.10) F	148–150	C <sub>12</sub> H <sub>15</sub> N <sub>7</sub> <sup>d</sup>
69			8.08 (0.02) 2	a	C <sub>11</sub> H <sub>13</sub> N <sub>7</sub> <sup>d</sup>

<sup>a-d</sup> See Table I.

Table III. 2-(Alkylamino)nicotinic Acids—SAR of the N Substituent

no.	R'	pA <sub>2</sub> <sup>a</sup>	mp <sup>b</sup> (°C)	formula <sup>c</sup>
32a	H	<6.0	a	C <sub>10</sub> H <sub>10</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32b	C <sub>2</sub> H <sub>5</sub>	8.77 (0.07) 2	188–191	C <sub>12</sub> H <sub>12</sub> N <sub>6</sub> O <sub>3</sub>
32c	C <sub>3</sub> H <sub>7</sub>	10.10 (0.08) F <sup>d</sup>	202–203	C <sub>13</sub> H <sub>14</sub> N <sub>6</sub> O <sub>3</sub>
32d	CH <sub>2</sub> CH=CH <sub>2</sub>	9.00 (0.07) 3	a	C <sub>12</sub> H <sub>12</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32e	CH <sub>2</sub> -c-C <sub>3</sub> H <sub>5</sub>	8.48 (0.01) 2	a	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub>
32f	C <sub>4</sub> H <sub>9</sub>	10.33 (0.03) 2	203–205	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub>
32g	CH <sub>2</sub> CH <sub>2</sub> CHMe <sub>2</sub>	8.96 (0.03) 2	212–213	C <sub>15</sub> H <sub>18</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32h	C <sub>6</sub> H <sub>11</sub>	9.07 (0.06) 2	92–93	C <sub>16</sub> H <sub>20</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>

<sup>a-d</sup> See Table I. <sup>e</sup> High-resolution MS within 0.004 of theory. <sup>f</sup> Combined calculation from 41 tissues.

1.39), and the ICI compound 7 (slope = 1.28) are noncompetitive antagonists.<sup>35</sup> The exocyclic alkylamino-linked heterocycles represented by A-81988, 16q, 20, 28b, and 24b represent a distinct class of angiotensin II antagonists.

Changing the 3-COOH in A-81988, or its *N*-butyl analog 32f, to other functional groups significantly reduced potency (Table V). The methyl ester 32z was less active by a factor of 1000, and the alcohol 32bb by a factor of 400. In the corresponding pyrimidines also containing an exocyclic *n*-propyl or *n*-butyl group, we also noted a similar loss in potency when the acid was converted to the ester and alcohol (data not shown). This contrasts with the results seen in the pyrimidine series containing a secondary exocyclic nitrogen (see Table II), where the esters 15c–d and alcohols 17c–d were only 3-fold weaker than the acids 16c–d. Similarly the alcohol DUP-753 (2b) is only 20-fold weaker than the corresponding acid (EXP-3174, 2c) (Table VIII). Other acidic groups [CH(OH)CH<sub>2</sub>COOH, CONHSO<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, OPO(OH)<sub>2</sub>, and NHSO<sub>2</sub>CF<sub>3</sub>, compounds 32gg, qq, nn, and rr of Table VI] imparted good activity, albeit not as potent as A-81988. Of the groups that are neutral at pH = 7.4, only the primary amide 32g and the aldehyde 32cc had pA<sub>2</sub> values greater than 8.0. Thus, a

Table IV. 2-(Alkylamino)nicotinic Acids—SAR of Substituents on the Pyridine Ring

no.	R	R'	pA <sub>2</sub> <sup>a</sup>	formula
32c	H	C <sub>3</sub> H <sub>7</sub>	10.10 (0.08) F <sup>d</sup>	C <sub>13</sub> H <sub>14</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32j	4-CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	9.64 (0.02) 2	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32k	5-CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	8.80 (0.09) 2	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32l	5-Cl	C <sub>3</sub> H <sub>7</sub>	9.07 (0.04) 2	C <sub>13</sub> H <sub>13</sub> ClN <sub>6</sub> O <sub>3</sub>
32m	5-F	C <sub>3</sub> H <sub>7</sub>	9.04 (0.02) 2	C <sub>13</sub> H <sub>13</sub> FN <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32n	5-I	C <sub>3</sub> H <sub>7</sub>	8.38 (0.15) F	C <sub>14</sub> H <sub>16</sub> IN <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32p	5-C <sub>6</sub> H <sub>5</sub>	C <sub>3</sub> H <sub>7</sub>	8.91 (0.20) 2	C <sub>20</sub> H <sub>20</sub> N <sub>6</sub> O <sub>3</sub> ·1.5H <sub>2</sub> O <sup>e</sup>
32q	5-NO <sub>2</sub>	C <sub>3</sub> H <sub>7</sub>	8.33 (0.03) 2	C <sub>14</sub> H <sub>14</sub> N <sub>6</sub> O <sub>3</sub> ·1.5H <sub>2</sub> O
32r	5-NH <sub>2</sub>	C <sub>3</sub> H <sub>7</sub>	7.60 (0.03) 2	C <sub>14</sub> H <sub>16</sub> N <sub>7</sub> O <sub>3</sub> <sup>d</sup>
32s	5-NHCOCH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	7.90 (0.02) 2	C <sub>15</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> ·1.33H <sub>2</sub> O
32t	6-CH <sub>3</sub>	C <sub>3</sub> H <sub>7</sub>	8.15 (0.07) 2	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub>
32u	6-F	C <sub>3</sub> H <sub>7</sub>	9.63 (0.30) 2	C <sub>14</sub> H <sub>14</sub> FN <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32w	6-CH <sub>3</sub> O	C <sub>3</sub> H <sub>7</sub>	7.78 (0.02) 3	C <sub>15</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>
32x	6-OH	C <sub>3</sub> H <sub>7</sub>	<6.0	C <sub>14</sub> H <sub>16</sub> N <sub>6</sub> O <sub>3</sub> <sup>d</sup>

<sup>a-d</sup> See Table I. <sup>e</sup> H: calcd, 5.65; found, 5.07. <sup>f</sup> See Table III.

second acidic group on the heterocycle is needed for high potency in our series, but one not required in compound 3, 6, and 7, (see Figure 1) all of which have similar potency to A-81988.

As observed with the pyrimidines, moving the ring nitrogen or the carboxylic acid relative to the exocyclic amine decreased in vitro potency (Table VI). Eliminating the ring nitrogen yielded the anthranilic acid 58, which was a very weak A-II antagonist.

Replacing the tetrazole in A-81988 with a carboxylic acid yielded compound 71 with a pA<sub>2</sub> = 7.49. Since the tetrazole is more acidic than the carboxylic acid, the salicylic acid analog 76 was prepared on the basis of the fact that salicylic acid is 15 times more acidic than benzoic acid.<sup>32</sup> However the salicylate 76 did not significantly improve the potency (pA<sub>2</sub> = 7.79), suggesting that the increased potency of the tetrazole relative to the carboxylic acid was not due solely to its greater acidity. Our results differ from the DUP-753 series where the carboxylic acid is only 20-fold less potent than the tetrazole, whereas in our compounds, the difference is a factor of 400.

**Radioligand Binding.** Our best compounds, A-81988 (32c) and the pyrimidine analog 16r, exhibited radioligand binding to angiotensin II (type I) receptors in rat liver in the nanomolar range, similar to that of the Merck compound, L-158809. A-81988 and three other compounds (16e, 16d, and 16k) were tested for binding to the angiotensin II (type 2) receptor in the bovine cerebellum and showed no binding at a 30 μM concentration. In general the pA<sub>2</sub> values correlate well with the binding data (see Table VIII).

**In Vivo Antihypertensive Activity.** Oral antihypertensive activity was assessed in various rat models (Table VIII). The pyrimidine ester 15c demonstrated oral activity at 10 mg/kg whereas the corresponding pyrimidine acid 16c, while more potent in vitro, showed no activity in the renal artery ligated hypertensive rat (RALHR) model. Compound 32c (A-81988) demonstrated oral activity for up to 24 hr in the RALHR model at 0.03 mg/kg, in the furosemide treated spontaneously hypertensive rat (FTSHR) model at 0.1 mg/kg, and in nontreated SHR

Table V. Pyridines—SAR of Substitution in the 3-Position

32

no.	X	R'	pA <sub>2</sub> <sup>a</sup>	mp <sup>b</sup> (°C)	formula <sup>c</sup>
32o	COOH	C <sub>2</sub> H <sub>7</sub>	10.10 (0.08) F <sup>e</sup>	202–203	C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sub>2</sub>
32f	COOH	C <sub>4</sub> H <sub>9</sub>	10.33 (0.03) 2	203–205	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sub>2</sub>
32y	CONH <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	8.58 (0.08) 2	194–197	C <sub>24</sub> H <sub>22</sub> N <sub>7</sub> O <sup>d</sup>
32z	COOCH <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	7.08 (0.15) 2	138–193	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sub>2</sub>
32aa	CN	C <sub>4</sub> H <sub>9</sub>	7.68 (0.18) 2	173–174	C <sub>24</sub> H <sub>22</sub> N <sub>7</sub> O-0.5H <sub>2</sub> O
32bb	CH <sub>2</sub> OH	C <sub>2</sub> H <sub>7</sub>	7.48 (0.01) 2	188–189	C <sub>22</sub> H <sub>24</sub> N <sub>6</sub> O-0.68H <sub>2</sub> O <sup>d</sup>
32cc	CHO	C <sub>2</sub> H <sub>7</sub>	8.58 (0.06) 2	a	C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sup>d</sup>
32dd	CH(OH)CH <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	7.26 (0.05) 2	83–85	C <sub>24</sub> H <sub>26</sub> N <sub>6</sub> O-0.5H <sub>2</sub> O
32ee	COCH <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	7.00 (0.05) 2	a	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sup>e</sup>
32ff	CH(OH)CH <sub>2</sub> COOEt	C <sub>2</sub> H <sub>7</sub>	7.88 (0.06) 2	a	C <sub>27</sub> H <sub>30</sub> N <sub>6</sub> O <sup>d</sup>
32gg	CH(OH)CH <sub>2</sub> COOH	C <sub>2</sub> H <sub>7</sub>	8.84 (0.01) 2	a	C <sub>24</sub> H <sub>26</sub> N <sub>6</sub> O <sub>2</sub> -0.5H <sub>2</sub> O
32hh	CONHSO <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>7</sub>	8.65 (0.02) 2	a	C <sub>28</sub> H <sub>27</sub> N <sub>7</sub> O <sub>2</sub> S <sup>d</sup>
32jj	CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	8.88 (0.02) 2	a	C <sub>24</sub> H <sub>26</sub> N <sub>6</sub> <sup>d</sup>
32kk	OH	C <sub>4</sub> H <sub>9</sub>	7.53 (0.03) 2	a	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sup>d</sup>
32mm	OCNHCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	7.34 (0.01) 2	a	C <sub>24</sub> H <sub>27</sub> N <sub>7</sub> O <sub>2</sub> -0.2CHCl <sub>3</sub> <sup>d</sup>
32nn	OP(O)(OH) <sub>2</sub>	C <sub>4</sub> H <sub>9</sub>	8.44 (0.10) 2	a	C <sub>22</sub> H <sub>26</sub> N <sub>6</sub> O <sub>4</sub> P <sup>e</sup>
32pp	OCOCH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	7.65 (0.12) 2	a	C <sub>22</sub> H <sub>26</sub> N <sub>6</sub> O <sub>3</sub>
32qq	CH <sub>2</sub> NHSO <sub>2</sub> CF <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	7.88 (0.07) 2	95–98	C <sub>24</sub> H <sub>26</sub> F <sub>3</sub> N <sub>7</sub> O <sub>2</sub> S <sup>d</sup>
32rr	NHSO <sub>2</sub> CF <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	9.27 (0.21) 2	214–216	C <sub>24</sub> H <sub>26</sub> F <sub>3</sub> N <sub>7</sub> O <sub>2</sub> S
32ss	NHSO <sub>2</sub> CH <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	7.98 (0.04) 2	137–140	C <sub>22</sub> H <sub>26</sub> N <sub>7</sub> O <sub>2</sub> S-0.5H <sub>2</sub> O <sup>d</sup>
32tt	NHCOCH <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	8.40 (0.06) 2	170–171	C <sub>24</sub> H <sub>26</sub> N <sub>7</sub> O <sup>d</sup>
32uu	NHCOCF <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	6.89 (0.04) 2	79–80	C <sub>24</sub> H <sub>26</sub> F <sub>3</sub> N <sub>7</sub> O-0.25H <sub>2</sub> O
32vv	NHCOCOOEt	C <sub>2</sub> H <sub>7</sub>	7.68 (0.11) 2	a	C <sub>28</sub> H <sub>27</sub> N <sub>7</sub> O <sub>3</sub> <sup>e</sup>
32ww	NHCOCOOH	C <sub>2</sub> H <sub>7</sub>	7.65 (0.12) 2	a	C <sub>24</sub> H <sub>26</sub> N <sub>7</sub> O <sub>3</sub> <sup>e</sup>
32xx	NHCONHCH <sub>3</sub>	C <sub>2</sub> H <sub>7</sub>	7.78 (0.04) 2	194–195	C <sub>24</sub> H <sub>26</sub> N <sub>6</sub> O-0.5H <sub>2</sub> O
32yy	NHCSNH <sub>2</sub>	C <sub>2</sub> H <sub>7</sub>	7.34 (0.30) 2	a	C <sub>22</sub> H <sub>24</sub> N <sub>6</sub> S-0.5H <sub>2</sub> O <sup>d</sup>
32zz	NO <sub>2</sub>	C <sub>2</sub> H <sub>7</sub>	7.92 (0.06) 4	176–178	C <sub>22</sub> H <sub>21</sub> N <sub>7</sub> O <sub>2</sub>

<sup>a-d</sup> See Table I. <sup>e</sup> High-resolution MS within 0.004 of theory. <sup>f</sup> See Table III.

Table VI. Pyridine and Benzene Carboxylic Acids—SAR of Positional Isomers

45, 42, 48, 58

no.	A	B	R'	pA <sub>2</sub> <sup>a</sup>	formula <sup>c</sup>
45			C <sub>2</sub> H <sub>5</sub>	8.12 (0.06) 2	C <sub>24</sub> H <sub>24</sub> N <sub>6</sub> O <sub>2</sub> <sup>d</sup>
42	N	CH	C <sub>2</sub> H <sub>7</sub>	7.23 (0.01) 2	C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sub>2</sub> -0.2H <sub>2</sub> O
48	CH	N	C <sub>2</sub> H <sub>7</sub>	8.45 (0.03) 2	C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sub>2</sub> -0.25H <sub>2</sub> O
58	CH	CH	C <sub>2</sub> H <sub>5</sub>	6.91 (0.06) 2	C <sub>22</sub> H <sub>22</sub> N <sub>6</sub> O <sub>2</sub> -0.25H <sub>2</sub> O

<sup>a-d</sup> See Table I.

Table VII. Comparison of A-81988 to Literature Standards

compd	pA <sub>2</sub> <sup>a</sup>	slope <sup>b</sup>
A-81988 (32c)	10.10 (0.08) F <sup>e</sup>	1.07 (0.03) <sup>e</sup>
DUP 753 (2b)	8.43 (0.20) F	1.01 (0.07)
L 158809 (3)	9.63 (0.07) F	1.37 (0.06)
	10.6	if slope is forced to unity <sup>c</sup>
DUP 532 (2d)	8.80 (0.14) F	1.81 (0.20)
EXP 3174 (2c)	9.71 (0.15) F	1.39 (0.19)
	11.0	if slope is forced to unity <sup>c</sup>
IC compd (7)	9.12 (0.27) F	1.28 (0.21)
	10.0	if slope is forced to unity <sup>c</sup>

<sup>a</sup> See Table I. <sup>b</sup> Standard error in parentheses. <sup>c</sup> This is calculated the same way as an estimated pA<sub>2</sub>. See Experimental Section. <sup>e</sup> See table III, footnote f.

at 3.0 mg/kg. No reduction in blood pressure was observed in normotensive rats at 3 mg/kg, po. The alcohol 32bb, the aldehyde 32cc, and the ester 32z, possible prodrugs of A-81988, were much less active. The *n*-butyl analog (32f) was slightly less active, while the pyrimidine 16r was 30-fold less active than A-81988 when given orally. Substitution on the pyridine ring with 4-Me, 5-F, or 6-F yielded compounds that were significantly less potent in reducing blood pressure in FTSHR when administered orally. The trifluoromethane sulfonamide 32rr, whose *in vitro* potency approached that of A-81988, was inactive in

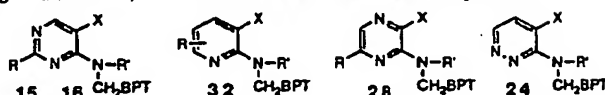
the RALHR at a 10-fold greater dose than that required to observe significant effects with A-81988. Compared to literature compounds, A-81988 was much more potent *in vivo* than DUP-753 (2b), and somewhat more potent than L-158809 (3). Pyridazine 24a and pyrazines 28a and 28b, while potent *in vitro*, were significantly weaker than A-81988 when administered orally.

**Pharmacokinetics.** The exceptional oral antihypertensive activity of A-81988 (32c) as compared to the pyrimidine analog 16r led us to initiate pharmacokinetic studies of the two compounds. A pharmacokinetic profile of L-158809 (3) was also determined so a comparison to a literature compound could be made.

The pharmacokinetic parameters for the A-II antagonists in normal male Sprague-Dawley rats are provided in Table IX. The pyrimidine A-II antagonist 16r was characterized by a low volume of distribution ( $V_1 = 0.08$  L/kg,  $V_\beta = 0.42$  L/kg) and a low plasma clearance [ $CL_p = 0.85 \pm 0.12$  mL/min (mean  $\pm$  SEM)] with a terminal elimination half-life of 1.5 h. Peak plasma concentrations ( $C_{max}$ ) ranged from 0.51 to 1.5 mcg/mL following 3.87–23.4 mg/kg single oral doses and calculated bioavailability values were 5–10%. The pyridine analogue, A-81988, provided a substantial improvement in the plasma elimination half-life (6–9 h following IV bolus administration) coupled with a 2–3-fold decrease in the apparent volume of distribution ( $V_1 = 0.04$  L/kg,  $V_\beta = 0.12$ –0.17 L/kg). The plasma clearance values averaged  $0.07 \pm 0.01$  mL/min over the *iv* dose range of 0.3–3 mg/kg. A-81988 was rapidly absorbed after oral dosing with peak plasma concentrations recorded in the first 1–2 h. Plasma concentrations increased with increasing dose, although the increase was not proportional to the dose. Bioavailability values in



Table VIII. Radioligand Binding and in Vitro, and in Vivo Data for Selected Compounds

							
no.	R	R'	X	pA <sub>2</sub> <sup>a</sup>	K <sub>i</sub> (nM) <sup>b</sup>	RALHR <sup>c</sup>	FT SHR <sup>d</sup>
15c	C <sub>2</sub> H <sub>5</sub>	H	COOEt	7.78	20.6 (5.54–77.0) 3	30, 32(±5)%, 2 10, 14(±8)%, 2	
16c	C <sub>2</sub> H <sub>5</sub>	H	COOH	8.30	68.1 (31.9–145) 3	3 (iv) inact	
16e	C <sub>4</sub> H <sub>9</sub>	H	COOH	7.91		3 (iv) inact	
16j	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	COOH	9.60	2.78 (1.66–4.64) 3	30, 18(±9)%, 2 10, 15(±2)%, 2	
16k	CH <sub>3</sub>	C <sub>4</sub> H <sub>9</sub>	COOH	8.81	15.3 (7.01–33.6) 3	30, 11(±10)%, 2	
16r	H	C <sub>4</sub> H <sub>9</sub>	COOH	9.57	1.77 (0.59–5.36) 3	10, 41(±6)%, 6 3, 18(±8)%, 4 1, 10(±4)%, 4	
32c	H	C <sub>2</sub> H <sub>5</sub>	COOH	10.10	0.61 (0.49–0.84) 3	1.0, 40(±4)%, 4 0.3, 36(±4)%, 7 0.01, 22(±6)%, 6 0.03, 10(±3)%, 7	1.0, 32(±1)%, 48(±2)%, 2 0.1, 23(±4)%, 36(±5)%, 6
32f	H	C <sub>4</sub> H <sub>9</sub>	COOH	10.33		0.3, 45(±7)%, 2 0.1, 16(±12)%, 2	0.3, 14(±3)%, 40(±4)%, 4 0.1, 5(±3)%, 22(±1)%, 4 1.0, 13(±3)%, 31(±6)%, 4 1.0, 10(±3)%, 15(±3)%, 3 1.0, 6(±4)%, 22(±4)%, 2 1.0, 15(±1)%, 36(±7)%, 2 1.0, inact
32d	H	CH <sub>2</sub> CH=CH <sub>2</sub>	COOH	9.00			
32j	4CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	COOH	9.64			
32m	5-F	C <sub>2</sub> H <sub>5</sub>	COOH	9.04			
32u	6-F	C <sub>2</sub> H <sub>5</sub>	COOH	9.63			
32z	H	C <sub>2</sub> H <sub>5</sub>	COOMe	7.08			
32bb	H	C <sub>2</sub> H <sub>5</sub>	CH <sub>2</sub> OH	7.48		0.3, inact	
32cc	H	C <sub>2</sub> H <sub>5</sub>	CHO	8.56		0.3, 15(±2)%, 2	
32rr	H	C <sub>2</sub> H <sub>5</sub>	NHSO <sub>2</sub> CF <sub>3</sub>	9.27		0.3, 6(±0)%, 2	
24a		C <sub>2</sub> H <sub>5</sub>	COOH	9.69			1.0, 3(±0)%, 18(±5)%, 2
28a	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	COOH	8.90			1.0, 2(±3)%, 18(±6)%, 2
28b	H	C <sub>4</sub> H <sub>9</sub>	COOH	9.70			1.0, 7(±1)%, 21(±6)%, 2
DUP-753 (2)				8.43	14.6 (9.53–22.4) 8	10, 27(±2)%, 7 3, inact	10, 21(±2)%, 34(±5)%, 4
L-158809 (3)				9.63 nc	0.45 (0.14–1.45) 3	3.0, 32(±9)%, 4 0.3, 25(±3)%, 4 0.1, 15(±2)%, 4 0.03, 8(±1)%, 4	1.0, 32(±5)%, 30(±8)%, 2
EXP-3174 (2c)				9.71 nc		10, 40(±8)%, 2	

<sup>a</sup> For standard errors and slope, see other tables. <sup>b</sup> K<sub>i</sub> (95% confidence limits), n. <sup>c</sup> Renal artery hypertensive rat model (dose in mg/kg), % decrease in bp at 4 h, (±SEM), number of rats. <sup>d</sup> Furosemide-treated spontaneous hypertensive rat model (dose in mg/kg), % decrease in bp at 4 h, (±SEM), % decrease in bp at 24 hr, (±SEM), number of rats.

Table IX. Pharmacokinetic Evaluation of Selected Angiotensin II Antagonists in Male Sprague-Dawley-Derived Rat

compd	intravenous dose						oral dose						
	dose (mg/kg)	$t_{1/2\beta}^a$ (h)	$V_1^b$ (L/kg)	$V_\beta^c$ (L/kg)	$CL_p^d$ (mL/min)	$n$	$t_{1/2\beta}^a$ (h)	$C_{max}^e$ ( $\mu$ g/mL)	$T_{max}^f$ (h)	$AUC_{0-\infty}^g$ ( $\mu$ g/hr/mL)	$F^h$ (%)	$n$	
3	3.87	4.5	0.41	1.78	1.47 (0.32)	4	3.9	1.59 (0.23)	2.0	11.14 (2.23)	66.7 (13.4)	4	
16r	3.87	1.5	0.08	0.42	0.85 (0.12)	3		0.51 (0.12)	1.3	2.38 (0.61)	10.3 (2.6)	7	
	10.0							0.84 (0.30)	0.9	2.83 (0.75)	4.8 (1.2) <sup>i</sup>	4	
	23.4							1.47 (0.28)	1.1	6.65 (0.81)	4.8 (0.6) <sup>i</sup>	4	
32c	0.1						$\leq 12$	0.49 (0.13)	1.3	8.21 (1.10)	97.9 (13.1) <sup>j</sup>	4	
	0.3	9.5	0.04	0.17	0.07 (0.01)	3	$> 12$	1.35 (0.10)	1.4	24.44 (2.62)	97.2 (10.4)	8	
	1.0	7.1	0.04	0.13	0.07 (0.01)	6	6.9	2.77 (0.54)	0.9	28.87 (7.69)	34.9 (9.3)	6	
	3.0	6.6	0.04	0.12	0.07 (0.01)	3	5.7	9.60 (0.98)	0.9	90.15 (32.25)	36.3 (13.0)	3	

<sup>a</sup> t<sub>1/2β</sub>, terminal elimination half-life. <sup>b</sup> V<sub>1</sub>, volume of distribution of the central compartment (= dose + the plasma concentration at time zero). <sup>c</sup> V<sub>β</sub>, volume of distribution of the terminal phase (= CL<sub>p</sub> + plasma elimination rate constant). <sup>d</sup> CL<sub>p</sub>, total plasma clearance (= dose + area under the curve, mean (SEM)). <sup>e</sup> C<sub>max</sub>, observed peak plasma concentration, mean (SEM). <sup>f</sup> T<sub>max</sub>, time of peak plasma concentration. <sup>g</sup> AUC, area under the curve, mean (SEM). <sup>h</sup> F, apparent bioavailability of the oral dose. <sup>i</sup> Bioavailability calculated from the 3.87 mg/kg intravenous dose. <sup>j</sup> Bioavailability calculated from the 0.3 mg/kg intravenous dose.

excess of 90% were observed in the 0.1 and 0.3 mg/kg dose groups, decreasing to ~35% at doses ≥1 mg/kg.

Compound 3 was characterized by a plasma elimination half-life (4.5 h) intermediate between compounds 16r and 32c. The volume of distribution values for compound 3 were 5–10 times greater than for compounds 16r and 32c. Due in part to the higher volume of distribution and plasma clearance values, the peak plasma concentrations for compound 3 were more than 7 times lower than those recorded for a 3 mg/kg oral dose of A-81988 (32c) in rat. A-81988 has a greater than 20-fold higher area under the curve than compound 3 after iv dosing in rat.

## Conclusion

We have discovered a novel series of potent, orally acting angiotensin II antagonists with high bioavailability typified by A-81988 (32c). Its unique structural feature is the presence of an alkylamino group linking the heterocyclic ring to the biphenyltetrazole moiety. Other six-membered ring heterocycles were also active if the ring nitrogen and the carboxylic acid are both situated ortho to the alkylamino group. All substitutions on the pyrimidine ring led to less active compounds. The carboxyl could be

replaced by other strongly acidic groups with slight loss in *in vitro* activity, but replacement by neutral groups led to a loss of activity.

### Experimental Section

**General.** Flash chromatography was done using silica gel (230–400 mesh) from E.M. Science. Proton NMR spectra were recorded on a General Electric QE300 instrument with Me<sub>4</sub>Si as an internal standard. Structure determination by X-ray crystallography was done on a Rigaku ASC-5 instrument. Elemental analyses were performed at Abbott Laboratories. Melting points were measured on a Thomas Hoover apparatus and are uncorrected.

**2-(Triphenylmethyl)-5-[(4'-(azidomethyl)biphenyl-2-yl)]-2H-tetrazole (11).** 2-(Triphenylmethyl)-5-[(4'-(bromomethyl)biphenyl-2-yl)]-2H-tetrazole (10)<sup>12</sup> (3.909 g, 7.02 mmol), was dissolved in 11 mL of DMF. Sodium azide (1.16 g, 17.8 mmol) was added and the mixture stirred 16 h at room temperature. Water was added to give a solid which was filtered, dissolved in chloroform, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated, and the residue was crystallized from ether and hexane to give 3.25 g (89% yield) of the title compound, mp 142–145 °C.

**2-(Triphenylmethyl)-5-[(4'-(aminomethyl)biphenyl-2-yl)]-2H-tetrazole (13).** Compound 11 (1.0 g, 1.93 mmol) in 14 mL of THF at 0 °C was treated with LiAlH<sub>4</sub> (0.173 g). After 30 min the reaction was worked up with 0.5 mL of water and 0.5 mL of 15% NaOH in the usual manner to give the title compound which was used as is.

**2-(Triphenylmethyl)-5-[(4'-(butylamino)methyl)biphenyl-2-yl)]-2H-tetrazole (12, R' = C<sub>4</sub>H<sub>9</sub>).** To 2-(triphenylmethyl)-5-[(4'-(bromomethyl)biphenyl-2-yl)]-2H-tetrazole (6.00 g, 10.7 mmol), dissolved in 55 mL of THF, was added 40 mL of butylamine. After 2 h at room temperature, the mixture was concentrated. The residue was dissolved in CHCl<sub>3</sub>, washed with dilute KOH and dried (K<sub>2</sub>CO<sub>3</sub>), and the solvents were removed to give the title compound which was used without further purification.

**Ethyl 2-Chloropyridine-3-carboxylate (29, R = H, R' = C<sub>2</sub>H<sub>5</sub>).** 2-Chloropyridine-3-carboxylic acid (25 g) was refluxed 3 h in 200 mL of benzene and 150 mL of SOCl<sub>2</sub>. The solution was concentrated and chased with toluene. The residue obtained was refluxed in 100 mL of ethanol for 20 min. The solvents were removed in vacuum to give the product which was used in the next step.

**Ethyl 2-(Propylamino)pyridine-3-carboxylate (30, R = H, R' = C<sub>2</sub>H<sub>5</sub>, R'' = C<sub>3</sub>H<sub>7</sub>).** The above chloro ester (7.00 g) was heated in a bomb with 12 mL of propylamine and 32 mL of ethanol for 6 h at 100 °C. The solution was concentrated, and the residue was dissolved in toluene, washed with dilute NaOH, dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and chromatographed, (8% EtOAc in hexane) to give 5.07 g of product in 68% yield.

**Ethyl 2-[N-Propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = H, R' = C<sub>2</sub>H<sub>5</sub>, R'' = C<sub>3</sub>H<sub>7</sub>).** Ethyl 2-(propylamino)pyridine-3-carboxylate (1.41 g, 6.78 mmol) in 3 mL of THF containing 2 mL of DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone) was treated at 0 °C with 6.78 mL of 1 M LiN(TMS)<sub>2</sub> in THF. After 10 min, 3.55 g (6.35 mmol) of bromomethyl compound 10 in 8 mL of THF was added dropwise. After 90 min at room temperature, toluene was added, along with 1 drop of concentrated HCl. The mixture was washed with water three times, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was chromatographed, (2.5% ether in toluene) to give 2.55 g of product, mp 129–131 °C (53% yield).

**Method A. Removal of the Triphenylmethyl Group on the Tetrazole.** Ethyl 2-[N-Propyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (32, X = COOEt, R = H, R' = C<sub>2</sub>H<sub>5</sub>). The above triphenylmethyl compound (2.00 g, 2.92 mmol) was dissolved in 24 mL of CH<sub>2</sub>Cl<sub>2</sub> and 36 mL of 88% HCOOH for 2 h at room temperature. The solvents were removed in vacuum, and the residue was stirred with 50% HCOOH. The resulting solid (triphenylmethanol) was filtered and washed with 50% HCOOH. The filtrate was concentrated and treated with water. This mixture was extracted with CHCl<sub>3</sub>. The CHCl<sub>3</sub> was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated,

and the residue was crystallized from ether to give 1.09 g (87%) of the desired compound, mp 143–144 °C.

**Method B. Hydrolysis of Heterocyclic Esters.** 2-[N-Propyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylic Acid (32c, X = COOH, R = H, R' = C<sub>2</sub>H<sub>5</sub>). The ethyl ester above (0.400 g, 0.905 mmol) was refluxed 90 min in 10 mL of ethanol and 2 mL of water containing 0.286 g of NaOH. Acetic acid (0.7 mL) was added, and the solution was concentrated. Water containing 0.7 mL of HCOOH was added, and the mixture was dissolved in CHCl<sub>3</sub>. This was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was crystallized from ether to give 0.278 g of product, mp 202–204 °C in 75% yield. <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 300 MHz): 0.73 (t, J = 7 Hz, 3H), 1.50 (m, 2H), 3.22 (q, J = 7 Hz, 2H), 4.67 (s, 2H), 6.80 (dd, J = 8, 4 Hz, 1H), 7.11 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 7.50–7.70 (m, 4H), 7.86 (dd, J = 4, 2 Hz, 1H), 8.21 (dd, J = 4, 2 Hz, 1H). Anal. (C<sub>26</sub>H<sub>22</sub>N<sub>6</sub>O<sub>2</sub>) C, H, N.

Pyrimidines with NH side chains can be hydrolyzed using this method, at room temperature, in 1 h. The pyrimidines unsubstituted in the 2-position, but having an N-alkyl, gave an unidentified impurity when hydrolyzed in refluxing EtOH-H<sub>2</sub>O, but this was largely eliminated by carrying out the hydrolysis in water at room temperature for 24 h.

**Ethyl 2-n-Butyl-4-[N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrimidine-5-carboxylate (14, R = C<sub>4</sub>H<sub>9</sub>, R' = H).** Ethyl 2-butyl-4-chloropyrimidine-5-carboxylate<sup>11</sup> (0.40 g, 1.65 mmol) was added to 13 dissolved in 4 mL of THF containing 0.5 g of triethylamine. After 2 h, CHCl<sub>3</sub> was added, the solution washed with NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated, and the residue chromatographed, eluting with 10% EtOAc in toluene to give 0.927 g of the title compound, crystallized from ether, mp 116–118 °C (69% yield). All other analogs of 14 could be prepared by this method, including N-alkyl compounds.

**2-Methoxypropionamidine Hydrochloride.** Methyl 2-methoxypropionimide hydrochloride<sup>16</sup> (53 g, 0.345 mol) in 400 mL of MeOH containing 70 mL of liquid NH<sub>3</sub> was kept at 25 °C for 16 h in an autoclave. The reaction mixture was concentrated, and the residue obtained was dissolved in 2-propanol and filtered from a small amount of insoluble material. The filtrate was concentrated and the residue crystallized from ether to give 47 g of the title compound.

**Ethyl 2-(2-Methoxyethyl)-4-hydroxypyrimidine-5-carboxylate.** To the above amidine (0.345 mol) dissolved in 200 mL of EtOH and cooled in ice was added slowly 223 g of a 21% solution of NaOEt in EtOH, followed by slow addition of 74.6 g (0.345 mol) of diethyl ethoxymethylene malonate. The solution was refluxed 2 h and then concentrated. Water was added, and the solution was neutralized with HCl and extracted with CHCl<sub>3</sub> four times. The organic extracts were dried (MgSO<sub>4</sub>) and concentrated, and the residue was crystallized from ether to give 58.5 g of the title product, mp 115–118 °C (75% yield).

**Ethyl 2-(2-Methoxyethyl)-4-[N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrimidine-5-carboxylate (14, R = MeOCH<sub>2</sub>CH<sub>3</sub>, R' = H).** To the above hydroxypyrimidine (1.85 g, 8.14 mmol) in 13 mL of CH<sub>2</sub>Cl<sub>2</sub>, containing 1.38 mL of Et<sub>3</sub>N, was added 1.025 g (8.96 mmol) of CH<sub>3</sub>SO<sub>2</sub>Cl with ice cooling. After 5 min of stirring a solution of 4.00 g (8.11 mmol) of 13 and 1.38 g of Et<sub>3</sub>N in 5 mL of CHCl<sub>3</sub> were added. After 1.5 h of stirring at room temperature, 50 mL of CH<sub>2</sub>Cl<sub>2</sub> was added and the solution was washed with NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), and concentrated. The residue was chromatographed (25% EtOAc in toluene) to give 4.815 g of the title compound, mp 128–130 °C (80% yield).

**Ethyl 3-Methyl-5-chloro-1,2,4-triazine-6-carboxylate.** To 3-methyl-5-hydroxy-1,2,4-triazine-6-carboxylate<sup>13</sup> (1.50 g, 8.20 mmol), suspended in 12 mL of POCl<sub>3</sub>, was added 0.827 g (8.20 mmol) of Et<sub>3</sub>N. After 1 h of stirring at room temperature, the mixture was concentrated, toluene was added, and the mixture was concentrated again. More toluene was added, and the solution washed with dilute NaHCO<sub>3</sub>, dried (MgSO<sub>4</sub>), and concentrated. The residue was dissolved in heptane, filtered from a small amount of insoluble material, and concentrated to give 1.30 g (6.47 mmol) of the title compound in 79% yield.

**Ethyl 3-Methyl-5-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-1,2,4-triazine-6-carboxylate (19).** To a solution of compound 12 (R' = C<sub>2</sub>H<sub>5</sub>)



(3.14 g, 5.87 mmol) in 8.5 mL of THF, containing 3.1 mL of Et<sub>3</sub>N, was added 1.30 g (6.47 mmol) of ethyl 3-methyl-5-chloro-1,2,4-triazine-6-carboxylate, prepared above. After 2 h of stirring at room temperature, the mixture was concentrated. The residue was dissolved in toluene, washed with NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was chromatographed (25% EtOAc in toluene) to give 3.91 g (95% yield) of the title compound, mp 178–179 °C.

**2,6-Dichloropyridazine-4-carboxylic acid.** 2,6-Dichloro-4-methylpyridazine<sup>17</sup> (10 g, 60 mmol) in 60 mL of concentrated H<sub>2</sub>SO<sub>4</sub> was treated with powdered K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> (21.2 g, 72 mmol), keeping the temperature between 35–40 °C. After 2 h, the mixture was poured into ice and extracted with 1 L of ether. The extracts were washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated, and the residue was crystallized from boiling water to yield 8.1 g of the title compound.

**Ethyl 2,6-Dichloropyridazine-4-carboxylate.** 2,6-Dichloropyridazine-4-carboxylic acid (7.1 g, 37 mmol) in 40 mL of THF with 5 mL of EtOH was treated with 500 mg of (dimethylamino)pyridine and 7.8 g (40 mmol) of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and stirred overnight at room temperature. The mixture was concentrated and partitioned between water and EtOAc. The organic phase was washed with water, NaHCO<sub>3</sub>, and NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was chromatographed (3:1 hexane/EtOAc) to give 5.00 g (61% yield) of the title compound.

**Ethyl 3-[N-Butyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-6-chloropyridazine-4-carboxylate (22).** The above ester (520 mg, 2.35 mmol), compound 12 (R' = C<sub>6</sub>H<sub>5</sub>) (1.26 g, 2.30 mmol), and 0.42 mL (3.0 mmol) of Et<sub>3</sub>N were refluxed together overnight. The reaction mixture was worked up as described for compound 19 and chromatographed (3:1 hexane/EtOAc) to give 1.35 (78%) of the title compound as an amorphous solid.

**Ethyl 3-[N-Butyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridazine-4-carboxylate (22, des chloro).** Compound 22, above, (610 mg, 0.83 mmol) was dissolved in 4:1 EtOAc/EtOH containing 140 mg of 10% Pd/C and 0.175 mL of Et<sub>3</sub>N (1.26 mmol). It was hydrogenated at atmospheric pressure for 24 h. The product was chromatographed (EtOAc in hexane) to give 260 mg of the title compound.

**Ethyl 2-Hydroxy-6-methylpyrazine-3-carboxylate (25).** Hydrogen chloride gas was bubbled 15 min through a mixture of 2-hydroxy-6-methylpyrazine-3-carboxylic acid<sup>22</sup> (32.5 g) suspended in 500 mL of EtOH and cooled in ice. This was stirred at room temperature overnight and then refluxed 2 h. The mixture was concentrated and the residue crystallized from ethanol in ether to give 21.48 g (58%) of 25, mp 153 °C.

**Ethyl 6-Methyl-2-[N-propyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrazine-3-carboxylate (26, R = CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub>).** To ester 25 (1.43 g, 7.86 mmol) in 8 mL of DMF, containing 1.8 g of Et<sub>3</sub>N, was added 1.45 g (8.21 mmol) of benzenesulfonyl chloride. After 5 min at room temperature 3.89 g (7.17 mmol) of 12 (R' = C<sub>6</sub>H<sub>5</sub>) in 3 mL of toluene was added, and the mixture stirred for 18 h at 45 °C. Dilute KHCO<sub>3</sub> was added, and the mixture was extracted with toluene. The product was purified by chromatography (16% EtOAc in toluene) to give 3.00 g (60%) of the title compound.

**Methyl 3-[N-Butyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyrazine-2-carboxylate (26, R = H, R' = C<sub>6</sub>H<sub>5</sub>).** Compound 27<sup>23</sup> (320 mg, 1.47 mmol), compound 12 (R' = C<sub>6</sub>H<sub>5</sub>) (825 mg, 1.50 mmol), and Et<sub>3</sub>N (0.225 g, 2.22 mmol) in 1.5 mL of THF were refluxed together for 5 h. The usual workup and purification by chromatography (3:1 hexane/EtOAc) gave 708 mg (70%) of the title compound.

**Methyl 2-[N-Propyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]-6-fluoropyridine-3-carboxylate (31, R = 6-F, R' = C<sub>6</sub>H<sub>5</sub>, R'' = CH<sub>3</sub>).** Methyl 2,6-difluoronicotinate<sup>14</sup> (86 mg, 0.5 mmol), compound 12 (R' = C<sub>6</sub>H<sub>5</sub>) (272 mg as the formate salt), and Et<sub>3</sub>N (0.14 mL, 1 mmol) were refluxed together overnight in 3 mL of THF. The residue, on workup, was chromatographed (20% EtOAc in hexane) giving 200 mg of product in 58% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): 0.76 (t, J = 7 Hz, 3H), 1.53 (dt, J = 7, 6.5 Hz, 2H), 3.22 (t, J = 7 Hz, 2H), 3.78 (s, 3H), 4.51 (s, 2H), 6.24 (dd, J = 9, 5 Hz, 1H), 6.85–6.95 (m, 6H), 6.95–7.10 (m, 4H), 7.20–7.50 (m, 11H), 7.90 (dd, J = 2, 7 Hz, 1H), 8.02 (dd, J = 9, 9 Hz, 1H).

**2-[N-Propyl-N-[[2'-[2-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-6-fluoropyridine-3-carboxylic Acid (32u) and 2-[N-Propyl-N-[[2'-[2-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]-6-methoxypyridine-3-carboxylic Acid (32w).** The trityl group was removed from 150 mg (0.218 mmol) of compound 31 (R = 6-F, R' = C<sub>6</sub>H<sub>5</sub>, R'' = CH<sub>3</sub>) using method A (above). The resulting product was refluxed for 2 h with 3 mL of 1:1 THF/MeOH and 1 mL of 4 N NaOH. The mixture was worked up according to method B, and the products were separated by preparative HPLC using a C<sub>18</sub> column, giving 17 mg of each compound.

**Ethyl 2-Chloro-5-fluoro-6-(methylthio)pyridine-3-carboxylate (35).** Ethyl 2,6-dichloro-5-fluoropyridine-3-carboxylate<sup>15</sup> (34, 1.00 g, 8.40 mmol) was stirred 3 h at room temperature with 589 mg (8.40 mmol) of NaSCH<sub>3</sub> in 4 mL of water and 4 mL of THF to give the title compound as a white solid. The structure was determined by X-ray crystallography.

**Ethyl 2-Chloro-5-fluoropyridine-3-carboxylate (29, R = 5-F).** Compound 35 (960 mg, 3.86 mmol) was refluxed 24 h with Raney nickel in EtOH. The product was chromatographed (5% EtOAc in hexane) to give 233 mg (30%) of the desired compound.

**Ethyl 5-Fluoro-2-[N-propyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = 6-F, R' = C<sub>6</sub>H<sub>5</sub>, R'' = C<sub>2</sub>H<sub>5</sub>).** Compound 29 (R = 5-F) (157 mg, 0.775 mmol) and 415 mg (0.775 mmol) amine 12 (R' = C<sub>6</sub>H<sub>5</sub>) were refluxed 18 h with 0.27 mL of Et<sub>3</sub>N, in 0.6 mL of THF, and worked up as before to give 59 mg (11%) of the title compound.

**Ethyl 2-Bromo-5-methylpyridine-3-carboxylate (29, R = 5-CH<sub>3</sub>, R'' = C<sub>2</sub>H<sub>5</sub>, 2-Br Analog).** A modification of the procedure of Baldwin<sup>16</sup> was used. C<sub>2</sub>H<sub>5</sub>CH=C(CN)COOEt (10.8 g, 69 mmol) in 50 mL of EtOH was treated dropwise with 9 mL (69 mmol) of DMF dimethyl acetal, and refluxed 18 h. The solvent was evaporated, and the residue was dissolved in 50 mL of acetic acid. HBr (100 mL, 30% in acetic acid) was added dropwise at 40 °C, and the mixture was heated at 60 °C for 6 h. The solvents were evaporated, the residue basified with NaHCO<sub>3</sub>, and extracted with EtOAc, and the product chromatographed (25% EtOAc in hexane) to give 2.50 g (15%) of title compound. This compound and the 4-methyl analog were reacted with propylamine and with 10 by the same method as the 2-Cl nicotinates.

**2-Hydroxy-5-nitropyridine-3-carboxylic acid (37).** Nitric acid (3 mL) was added dropwise to 7.0 g of 2-hydroxynicotinic acid in 50 mL of sulfuric acid at 0 °C. The solution was stirred at room temperature 16 h and at 50–70 °C 1.5 h. Pouring the mixture on to ice gave 7.3 g (87%) of 37.

**Ethyl 2-Chloro-5-nitropyridine-3-carboxylate (29, R = 5-NO<sub>2</sub>).** A 5.00-g sample of the above hydroxy compound was refluxed 2 h with 32 mL of thionyl chloride containing 2 mL of DMF. The solution was concentrated, and the residue was treated with 20 mL of ethanol to give 5.04 g (81%) of the desired compound. This compound reacted with amine 12 at room temperature in 3 h.

**Methyl 2-Hydroxy-5-iodopyridine-3-carboxylate (38).** Methyl 2-hydroxynicotinate (1.7 g, 11.1 mmol) and 3.25 g (14.4 mmol) N-iodosuccinimide were refluxed in 40 mL of CH<sub>2</sub>Cl<sub>2</sub> in the dark for 48 h. The solution was washed with sodium thiosulfate twice, brine once, and dried (Na<sub>2</sub>SO<sub>4</sub>) to give 2.79 g (90%) of 38.

**Methyl 2-Chloro-5-iodopyridine-3-carboxylate (29, R = 5-I, R'' = CH<sub>3</sub>).** Compound 38 (500 mg) was refluxed 7 h in 5 mL of POCl<sub>3</sub>. Working up the reaction in the usual manner and purifying the product by chromatography (10% EtOAc in hexane) gave 368 mg (69%) of the title compound.

This compound reacts with 12 by refluxing in THF with Et<sub>3</sub>N overnight to give 31 (5-I) in 40% yield.

**Methyl 5-Phenyl-2-[N-propyl-N-[[2'-[2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate (31, R = 5-C<sub>6</sub>H<sub>5</sub>, R'' = CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub>).** To a solution of 5 mg of (Ph<sub>3</sub>P)<sub>2</sub>Pd in 2 mL of toluene was added 48 mg (60 μmol) of 31 (R = 5-I). After 10 min of stirring, 2 mL of nitrogen-sparged 2 N Na<sub>2</sub>CO<sub>3</sub> solution was added, followed by 9 mg (70 μmol) of phenylboronic acid (all with careful exclusion of air). The mixture was refluxed 2 h, cooled, and partitioned between ether and water. The organic layer was washed with 1 N H<sub>3</sub>PO<sub>4</sub> and then NaCl, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The

product was chromatographed (20% EtOAc in hexane) to give the title compound.

**Methyl 2,5-Dichloropyridine-3-carboxylate** (29, R = 5-Cl, R' = CH<sub>3</sub>). 2-Hydroxynicotinic acid (13.9 g, 0.10 mol) was added to an ice-cooled solution of sodium hypochlorite (170 mL, 0.12 mol) and 32 g of 50% NaOH, and stirred overnight at room temperature. Sodium sulfite (1.4 g) in 5 mL of water was added, and the mixture was acidified with 50 mL of concentrated HCl. The resulting solid was filtered, washed with water and then acetone, and dried in vacuo at 65 °C overnight to give 14.2 g of 5-chloro-2-hydroxynicotinic acid. This acid (5.00 g, 0.029 mol) was refluxed 2 h with 32 mL of thionyl chloride and 2 mL of DMF. The mixture was concentrated and treated with 25 mL of MeOH. After workup the product was purified by chromatography (10% EtOAc in hexane) to get 4.16 g (70%) of the title compound.

This compound was reacted with propylamine and then with 10 by the same method that was used with ethyl 2-chloronicotinate.

**Methyl (and Benzyl) 6-Benzyl-2-[N-propyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate** (32, R = 6-C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>O-, R' = C<sub>6</sub>H<sub>5</sub>, X = COOEt). Benzyl alcohol (142 mg, 1.31 mmol) was converted to its sodium salt by stirring with 56 mg of 60% dispersion of NaH (1.40 mmol) in 0.6 mL of DMF for 1 h at room temperature. A solution of the 6-F compound (32u, methyl ester, 148 mg, 0.327 mmol) in 1.4 mL of DMF was added. The mixture was stirred at 25 °C for 18 h and at 60 °C for 6 h. The solvent was removed under high vacuum, and the residue was partitioned between 10 mL of 0.1 M NaHSO<sub>4</sub> and 20 mL of CH<sub>2</sub>Cl<sub>2</sub>. The product was purified by chromatography (EtOAc/hexane 1:2) to give 113 mg of an equal mixture of methyl and benzyl esters.

**6-Hydroxy-2-[N-propyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylic Acid** (32x). The above mixture of esters (110 mg, 0.188 mmol) was hydrolyzed with 0.75 mL of aqueous NaOH in 2 mL of methanol at 70 °C for 18 h to give 75% of the 6-(benzoyloxy) carboxylic acid. This was hydrogenated over 10% Pd/C (35 mg) in 5 mL of EtOAc and 0.7 mL of Et<sub>3</sub>N for 27 h at 1 atm H<sub>2</sub>. The product was purified by preparative TLC (5% MeOH, 1% HOAc in CH<sub>2</sub>Cl<sub>2</sub>) to give 20.3 mg (41%) of 32x.

**Ethyl 5-Amino-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate** (31, R = 5-NH<sub>2</sub>, R' = C<sub>6</sub>H<sub>5</sub>, R'' = C<sub>6</sub>H<sub>5</sub>). Compound 31 (R = 5-NO<sub>2</sub>) (500 mg, 0.69 mmol) in 5 mL of EtOAc was hydrogenated at 1 atm for 10 h over 75 mg 10% Pd/C to give 395 mg (82%) of the title compound.

**Ethyl 5-(Acetylamino)-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate** (31, R = 5-AcNH, R' = C<sub>6</sub>H<sub>5</sub>, R'' = C<sub>6</sub>H<sub>5</sub>). Compound 31 (R = 5-NH<sub>2</sub>) (50 mg) was stirred overnight with 1 mL of CHCl<sub>3</sub>, 0.1 mL of Et<sub>3</sub>N, and 0.2 mL of acetic anhydride. Workup and purification by chromatography (25% EtOAc in hexane) gave the title compound.

**Methyl 4-[N-Propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxylate** (41). 4-Chloronicotinic acid<sup>19</sup> was converted to the methyl ester (40) in 85% yield with diazomethane. This ester (700 mg, 4.08 mmol), amine 12 (R = C<sub>6</sub>H<sub>5</sub>), and Et<sub>3</sub>N (1.1 mL, 7.89 mmol) in 10 mL of 2-propanol were heated in a sealed tube at 120 °C for 6 h. The product was worked up as described for the 2-amino isomer to give 454 mg (25%) of 41.

**Ethyl 2-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-5-carboxylate** (44, R' = C<sub>6</sub>H<sub>5</sub>). 6-Chloronicotinic acid was esterified by the method used for 2,6-dichloropyridazine-4-carboxylate, described above. This chloro ester was reacted with butylamine by the method used for ethyl 2-chloronicotinate, and the resulting ethyl 6-(butylamino)nicotinate reacted with 10 in a similar manner to give the title compound in 67% yield.

**Ethyl 3-(Propylamino)pyridine-4-carboxylate**. 3-Aminopyridine-4-carboxylic acid<sup>20</sup> (2.00 g) was esterified by warming on a steam bath with 4 g of ethanol and 4.0 g of H<sub>2</sub>SO<sub>4</sub> for 4 h. To this ester (750 mg, 4.52 mmol), in 35 mL of THF containing 1.30 mL of DMPU at 0 °C, was added 4.7 mL of 1 M lithium hexamethyl disilazide. After 30 min of stirring at 0 °C, 0.80 mL (9.24 mmol) of allyl bromide was added. The mixture was stirred at room temperature overnight and worked up as usual. The

product was chromatographed (1:5 EtOAc/hexane) to give 465 mg of the 3-allylamino compound. This was hydrogenated in 25 mL of EtOAc over 55 mg of PtO<sub>2</sub> to give 448 mg of the title compound.

**Ethyl 3-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-4-carboxylate** (47, R = C<sub>6</sub>H<sub>5</sub>). The 3-propylamino compound described above (405 mg, 1.95 mmol) was alkylated with 10 using the method used to convert 30 to 31. The product was purified by chromatography, giving 190 mg (14%) of the title compound.

**Ethyl 2-(Butylamino)pyrimidine-5-carboxylate** (50). Ethyl 2-(ethylthio)pyrimidine-5-carboxylate<sup>21</sup> (974 mg, 4.6 mmol) was heated in a sealed tube for 3 h with 2 mL of butylamine and 4 mL of EtOH. The solution was concentrated, and the residue was partitioned between NaHCO<sub>3</sub> solution and EtOAc. The product was purified by chromatography (20% EtOAc in hexane) to give 850 mg of the desired product as a white solid.

**Ethyl 2-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrimidine-5-carboxylate** (51). Compound 50 (573 mg, 2.57 mmol) was reacted with 1.43 g (2.57 mmol) of 10 using the method used to convert 30 to 31. The yield was 1.20 g (67%).

**Methyl 2-Chloro-4-[N-butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrimidine-6-carboxylate**. Methyl 2,4-dichloropyrimidine-6-carboxylate<sup>21</sup> (220 mg, 1.06 mmol), 1 mL of Et<sub>3</sub>N, amine 12 (R = C<sub>6</sub>H<sub>5</sub>) (495 mg, 0.90 mmol), and 2 mL of DMF were stirred at 25 °C for 15 min. The mixture was dissolved in EtOAc, washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The product was purified by chromatography (3% EtOAc in CH<sub>2</sub>Cl<sub>2</sub>) to give 500 mg of the title compound.

**4-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyrimidine-6-carboxylic Acid** (55, R' = C<sub>6</sub>H<sub>5</sub>). The 2-chloropyrimidine synthesized above (880 mg, 1.2 mmol) in 8 mL of THF was hydrogenated over 1.30 g of 10% Pd/C at 1 atm for 24 h. The triphenylmethyl group was removed, and the ester was hydrolyzed as described by the general methods A and B to give 185 mg (40%) of the title compound. NMR showed that the compound was a 4-aminopyrimidine rather than a 2-aminopyrimidine. NMR (DMSO-d<sub>6</sub>): 0.90 (t, J = 7.5 Hz, 3H), 1.30 (m, 2H), 1.50 (m, 2H), 3.55 (bs, 2H), 4.87 (bs, 2H), 7.05 (d, J = 8 Hz, 2H), 7.15 (d, J = 8 Hz, 2H), 7.52-7.68 (m, 4H), 7.82 (s, 1H), 8.60 (s, 1H).

**Ethyl 1-(Butylamino)benzene-2-carboxylate**. Ethyl anthranilate (4.96 g, 30 mmol), K<sub>2</sub>CO<sub>3</sub> (13.8 g, 100 mmol), and butyl iodide (25 mL) were stirred at room temperature 48 h and then refluxed 8 h. The mixture was diluted with EtOAc, filtered, and concentrated. The residue was chromatographed (EtOAc in hexane) to give 2.20 g (33%) of the desired product as a yellow liquid.

**Ethyl 1-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]benzene-2-carboxylate** (57). Ethyl 1-(butylamino)benzene-2-carboxylate (2.00 g, 9.0 mmol), K<sub>2</sub>CO<sub>3</sub> (1.38 g, 10 mmol), and 10 (2.00 g, 3.0 mmol) were stirred in 3 mL of DMF at 55 °C for 20 h. The product was chromatographed (EtOAc in hexane) to get 800 mg (46%) of the title compound.

**3-(Hydroxymethyl)-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59, X = CH<sub>2</sub>OH, R' = C<sub>6</sub>H<sub>5</sub>). Ester 31 (R = H, R' = C<sub>6</sub>H<sub>5</sub>, R'' = C<sub>6</sub>H<sub>5</sub>) (2.574 g, 3.758 mmol) in 20 mL of THF at 0 °C was treated with 500 mg (13.2 mmol) of LiAlH<sub>4</sub>. After 2 h the reaction was subject to a basic workup. The product was chromatographed (22% EtOAc in hexane) to give 2.290 g (95%) of the title compound.

**2-[N-Propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxaldehyde** (59, X = CHO, R' = C<sub>6</sub>H<sub>5</sub>). Alcohol 59 (X = CH<sub>2</sub>OH, R' = C<sub>6</sub>H<sub>5</sub>) (1.0123 g, 1.575 mmol) and activated manganese dioxide (3.00 g, 34.5 mmol) were stirred at room temperature 20 h. The solids were filtered and the solution concentrated. The residue was chromatographed (20% EtOAc in hexane) to give 0.946 g (96%) of the title compound.

**3-(1-Hydroxyethyl)-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59, X = CH(OH)CH<sub>3</sub>, R' = C<sub>6</sub>H<sub>5</sub>). Aldehyde 59 (X = CHO, R' = C<sub>6</sub>H<sub>5</sub>) (172.5 mg, 0.269 mmol) in 3 mL of THF was

treated with 1.5 M methylmagnesium bromide in THF (0.27 mL, 0.41 mmol). After 15 min, the reaction was quenched with  $\text{NH}_4\text{Cl}$ . Chromatography (25% EtOAc in hexane) gave 164.5 (93%) of the title compound.

**3-Acetyl-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{COCH}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Alcohol 59 ( $\text{X} = \text{CH}(\text{OH})\text{CH}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ) (108.6 mg, 0.163 mmol) in 7 mL of  $\text{CH}_2\text{Cl}_2$  was added to 1,1,1-tris(acetoxy)-1,1-dihydro-1,2-benziodoxol-3(1H)-one<sup>24</sup> (220 mg, 0.519 mmol). After 30 min of stirring at room temperature, the mixture was chromatographed (20% EtOAc in hexane) to get 65.7 mg (62%) of the title compound.

**3-[2-(Ethoxycarbonyl)-1-hydroxyethyl]-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{CH}(\text{OH})\text{CH}_2\text{COOEt}$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). *n*-Butyllithium in hexane (1.3 M, 0.70 mL, 0.90 mmol) was added to diisopropylamine (0.150 mL, 1.07 mmol) in 8 mL of THF at 0 °C. After 15 min, the mixture was cooled to -78 °C and treated with ethyl acetate (0.090 mL, 0.93 mmol). After 20 min, aldehyde 59 ( $\text{X} = \text{CHO}$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ) (515 mg, 0.804 mmol) was added and the reaction stirred at -78 °C for 45 min. The reaction was quenched with  $\text{NaHCO}_3$  solution. Chromatography (30% EtOAc in hexane) gave 556 mg (97%) of the title compound.

**N-(Benzenesulfonyl)-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxamide** (59,  $\text{X} = \text{CONHSO}_2\text{C}_6\text{H}_5$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 31 ( $\text{R} = \text{H}$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ,  $\text{R}'' = \text{C}_2\text{H}_5$ ) was hydrolyzed using method B, without using the  $\text{HCOOH}$  to give the triphenylmethyl-protected acid. This acid (930 mg, 1.42 mmol) was stirred 1 h at room temperature with 678 mg (5.7 mmol) of thionyl chloride in 2 mL of  $\text{CH}_2\text{Cl}_2$ . The solvents were evaporated and benzene sulfonamide (1.3 g, 8.5 mmol) was added. The reaction was cooled to -78 °C and 2 mL of  $\text{Et}_3\text{N}$  was added, and the mixture was stirred overnight at room temperature. The product was purified by chromatography (1:1 EtOAc/hexane) to give 390 mg (35%) of the title compound.

**2-(Butylamino)pyridine-3-carbonitrile**. 2-Chloropyridine-3-carbonitrile (1.30 g, 9.60 mmol) was refluxed overnight with 3 mL of *n*-butylamine in 10 mL of isopropyl alcohol. The product was purified by chromatography (2:1 hexane/EtOAc) to give 1.6 g (95%) of the desired product.

**2-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carbonitrile** (59,  $\text{X} = \text{CN}$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). 2-(Butylamino)pyridine-3-carbonitrile (1.60 g, 9.14 mmol) and 10 (5.32 g, 9.55 mmol) were reacted by the method used to convert 30 to 31. The product was chromatographed (25% ether in hexane) to give 3.60 g (60%) of the title compound.

**2-[N-Butyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine-3-carboxamide** (32y). Compound 32aa (100 mg) was refluxed in 3 mL of EtOH and 3 mL of 10% KOH in water, for 16 h. The solution was concentrated, water and  $\text{HCOOH}$  were added, and the resulting oil was chromatographed (2.5%  $\text{HCOOH}$ , 2.5% water in EtOAc) to give 55 mg (54%) of the title compound, mp 194–197 °C.

**3-(Aminomethyl)-2-[N-butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{CH}_2\text{NH}_2$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Nitrile 59 ( $\text{X} = \text{CN}$ ) (1.52 g, 2.33 mmol) in 50 mL of ether and 0.26 g of  $\text{LiAlH}_4$  were refluxed 1 h. Basic workup gave 1.20 g (79%) of the title compound which was used directly in the next step.

**3-[(Trifluoromethanesulfonamido)methyl]-2-[N-butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{CH}_2\text{NHSO}_2\text{CF}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). To the aminomethyl compound described above (330 mg, 0.504 mmol), in 20 mL of  $\text{CH}_2\text{Cl}_2$  containing 0.13 g of 2,6-di-*tert*-butyl-4-methylpyridine, cooled to -20 °C, was added 0.11 mL (0.655 mmol) of trifluoromethanesulfonic anhydride. After 2 h of stirring at -20 °C, the mixture was washed with  $\text{NaHCO}_3$ , and the residue was chromatographed (30% EtOAc in hexane) to get 140 mg (40%) of the title compound.

**3-Nitro-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NO}_2$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). 2-Chloro-3-nitropyridine (1.29 g, 8.14 mmol) was refluxed 2.5 h with amine 12 ( $\text{R}' = \text{C}_6\text{H}_5$ ) (4.03 g, 7.53 mmol) in 8 mL of THF containing 2.5 mL of  $\text{Et}_3\text{N}$ . The solution was concentrated and the residue dissolved in toluene, washed with

$\text{NaHCO}_3$ , and dried ( $\text{Na}_2\text{SO}_4$ ). Chromatography (25% EtOAc in toluene) gave 4.35 g (88%) of the title compound, mp 104–106 °C.

**3-Amino-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NH}_2$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NO}_2$ ) (2.00 g) in 250 mL of EtOAc was hydrogenated over 200 mg of 10% Pd/C at 4 atm for 2 h to give 1.2 g (60%) of the title compound, after chromatography (25% EtOAc in hexane).

**3-[(Methylamino)carbonyl]amino-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NHCONHCH}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (830 mg, 1.0 mmol) in 5 mL of  $\text{CH}_2\text{Cl}_2$  was treated with 65 mg (1.14 mmol) of methyl isocyanate. After stirring overnight, the product was chromatographed (50% EtOAc in hexane) to give 390 mg (50%) of the title compound.

**3-(Acetylamino)-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NHCOCH}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (500 mg, 0.796 mmol) was stirred overnight with 0.30 mL of acetic anhydride in 10 mL of pyridine. The mixture was concentrated and the product chromatographed (20% EtOAc in hexane) to give 400 mg (78%) of the title compound.

**3-[(Trifluoroacetyl)amino]-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NHCOCF}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (100 mg, 0.16 mmol) was stirred for 1 h with 34  $\mu\text{L}$  (0.24 mmol) of trifluoroacetic anhydride and 25.7  $\mu\text{L}$  of pyridine in 5 mL of  $\text{CH}_2\text{Cl}_2$ . The mixture was concentrated and chromatographed (17% EtOAc in hexane) to get 100 mg (86%) of the title compound.

**3-Methanesulfonamido-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NHSO}_2\text{CH}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (500 mg, 0.8 mmol) was stirred 18 h with 0.92 mL (1.04 mmol) of methanesulfonyl chloride and 0.11 mL of  $\text{Et}_3\text{N}$  in 10 mL of  $\text{CH}_2\text{Cl}_2$ . Chromatography (25% EtOAc in hexane) gave 30% of the title compound.

**3-(Trifluoromethanesulfonamido)-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NHSO}_2\text{CF}_3$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (250 mg, 0.40 mmol) was stirred for 1 h at -20 °C with 84  $\mu\text{L}$  of trifluoromethanesulfonic anhydride and 110 mg of 2,6-di-*tert*-butyl-4-methylpyridine. The mixture was washed with  $\text{NaHCO}_3$ , dried, and concentrated to give the title compound in 70% yield.

**3-Thioureido-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NHCSNH}_2$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (200 mg, 0.329 mmol) in 3.2 mL of THF at -78 °C was treated with 0.335 mL (0.335 mmol) of 1 M sodium hexamethyl disilazide in THF. After 30 min at -78 °C, 40 mg (0.350 mmol) thiophosgene was added. The red solution was stirred for 30 min at 0 °C and then treated with aqueous ammonia. This mixture was stirred 30 min at room temperature. The solution was concentrated, and the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The product was purified by chromatography (40% EtOAc in hexane) to give 160 mg (73%) of the title compound.

**3-[(Ethoxycarbonyl)carbonyl]amino-2-[N-propyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl]methyl]amino]pyridine** (59,  $\text{X} = \text{NECOCOEt}$ ,  $\text{R}' = \text{C}_6\text{H}_5$ ). Compound 59 ( $\text{X} = \text{NH}_2$ ) (150 mg, 0.24 mmol), in 6 mL of  $\text{CH}_2\text{Cl}_2$  containing 0.1 mL of  $\text{Et}_3\text{N}$ , at 0 °C, was treated with 54 mg (0.48 mmol) of ethyl oxalyl chloride and stirred 2 h. The mixture was concentrated, and the residue was chromatographed (15% EtOAc in hexane) to give 149 mg (85%) of the title compound. In the preparation of the diacid 32ww, the ester hydrolysis (method B) was carried out at room temperature for 18 h.

**3-(Benzyloxy)-2-(butylamino)pyridine** (64). To 2-amino-3-(benzyloxy)pyridine (63, Aldrich, 2.50 g, 12.5 mmol) in THF at 0 °C was added 12.5 mL of 1 M lithium hexamethyl disilazide in THF. After 30 min at room temperature, 2.30 g (12.5 mmol) of *n*-butyl iodide was added and the mixture stirred overnight at room temperature. After workup, the product was purified by chromatography (10% EtOAc in hexane) and gave 2.75 g (86%) of the title compound.

**3-(Benzoyloxy)-2-[N-butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl]biphenyl-4-yl)methyl]amino]pyridine (59, X = OCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, R' = C<sub>6</sub>H<sub>5</sub>).** Compound 64 (1.35 g, 5.3 mmol) was reacted with 10 (3.54 g, 5.3 mmol) by the same method as 64 itself was prepared (above). The product was purified by chromatography (10% EtOAc in hexane) to give 2.40 g (62%) of the title compound.

**3-Hydroxy-2-[N-butyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]pyridine (32kk).** The compound above was detritylated by method A in 76% yield. This compound (200 mg, 0.41 mmol) was hydrogenated for 7 h at 1 atm at room temperature in 100 mL of EtOAc containing 3 mL of Et<sub>3</sub>N, using 100 mg of 10% Pd/C as catalyst. The product was purified by chromatography (5% MeOH, 0.5% AcOH, in CHCl<sub>3</sub>) to get 158 mg (96%) of 32kk.

**3-Acetoxy-2-[N-butyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]pyridine (32pp).** Compound 32kk (75 mg, 0.19 mmol) in 2 mL of DMF and 2 mL of pyridine was treated with 2 drops of acetic anhydride. After 1 h of stirring at room temperature, the solution was concentrated, dissolved in ether, washed with water, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give 41 mg (63%) of 32pp.

**3-[(Methylamino)carbonyloxy]-2-[N-butyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]pyridine (32mm).** To compound 32kk (32 mg, 0.08 mmol), in 1 mL of DMF and 0.2 mL of Et<sub>3</sub>N, were added two drops of methyl isocyanate. After 2 h, the solution was concentrated and the residue chromatographed (5% MeOH, 0.5% AcOH in CHCl<sub>3</sub>) to get 16 mg (49%) of 32mm.

**2-[N-Butyl-N-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]pyridine-3-yl Phosphate (32nn).** Compound 32kk (25 mg, 0.06 mmol) was stirred 2.5 h with 0.5 mL of pyridine and 3 drops of POCl<sub>3</sub>. After cooling to 0 °C, 10 drops of water and 3 drops of 1 N NaOH were added, and then the solution was stirred at room temperature for 1 h. The product was purified by reverse-phase HPLC, eluting with a gradient of 0 to 70% acetonitrile in 0.1% aqueous trifluoroacetic acid to afford 4 mg (15%) of 32nn.

**2-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]-4,6-dimethylpyrimidine (Trityl 67).** 2-(Butylamino)-4,6-dimethylpyrimidine<sup>28</sup> (968 mg, 5.41 mmol) was reacted with 10 (2.52 g, 4.52 mmol) using the method used to convert 30 to 31. The product was purified by chromatography (2% ether in toluene), giving 1.65 g (55%) of the title compound, mp 131–133 °C.

**4-[N-Butyl-N-[[2'-(2-(triphenylmethyl)-2H-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]-2,6-dimethylpyrimidine (Trityl 65).** 4-(Butylamino)-2,6-dimethylpyrimidine<sup>28</sup> (806 mg, 4.50 mmol) was reacted with 10 (2.10 g, 3.76 mmol) using the method used to convert 30 to 31. The product was purified by chromatography (40% EtOAc in toluene), giving 1.55 g (63%) of the title compound, mp 125–127 °C.

**2-[N-Propyl-N-[[2'-(2-(triphenylmethyl)-tetrazol-5-yl)biphenyl-4-yl)methyl]amino]pyrimidine (Trityl 69).** 2-Bromopyrimidine (1.00 g, 6.28 mmol), amine 12 (R' = C<sub>6</sub>H<sub>5</sub>) (2.00 g, 3.74 mmol), and diisopropyl ethylamine (1.00 g, 7.75 mmol) were refluxed 10 h in 3.5 mL of acetonitrile. Toluene was added and the mixture washed with NaHCO<sub>3</sub>, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. Chromatography (4% EtOH in toluene) gave 1.64 g (71%) of the title compound, mp 133–134 °C.

**Methyl 2-[N-Propyl-N-[[2'-(2-carbomethoxybiphenyl-4-yl)methyl]amino]pyridine-3-carboxylate (71, R = CH<sub>3</sub>).** Methyl (2-propylamino)nicotinate (30) (194 mg, 1.0 mmol) was reacted with bromide 70<sup>12</sup> (381 mg, 1.0 mmol); using the same method described above in which 30 was reacted with 10 to give 31. The product was purified by chromatography (30% EtOAc in hexane) to give 367 mg (88%) of 71 (R = CH<sub>3</sub>).

**Methyl 2-Hydroxy-6-(benzyloxy)benzoate.** 2,6-Dihydroxybenzoic acid was esterified with diazomethane in 60% yield. This ester (500 mg, 2.97 mmol) in 5 mL of THF was added to a suspension of sodium hydride (120 mg of 60% dispersion washed with THF, 2.97 mmol) in 2 mL of THF. After 10 min benzyl bromide (0.354 mL, 2.97 mmol) and 5 mg of tetrabutylammonium iodide were added. After 2 h of refluxing, the solution was added to NaHCO<sub>3</sub> solution, and extracted with EtOAc. The product was purified by chromatography (10% ether in hexane) to yield 230 mg (30%) of the title compound.

**Methyl 2-Trifluoro-6-(benzyloxy)benzoate (73).** To a stirred solution of the above phenol (230 mg, 0.89 mmol), in 1.2 mL of CH<sub>2</sub>Cl<sub>2</sub> containing 0.35 (4.45 mmol) pyridine, and cooled to 0 °C, was added 0.18 mL (1.02 mmol) of trifluoromethanesulfonic anhydride. After 30 min at 0 °C and 2 h at room temperature, ether was added and the solution washed with NaHCO<sub>3</sub>, water, 3 N HCl, and again water and dried (MgSO<sub>4</sub>). After concentration, the residue was chromatographed (18% ether in hexane) to yield 177 mg (51%) of 73.

**Methyl 2-(Benzoyloxy)-4'-methylbiphenyl-2-carboxylate (74).** To a stirred solution of 73 (498 mg, 1.26 mmol) in 3 mL of toluene was added 64 mg (0.06 mmol) of (Ph<sub>3</sub>P).Pd. After 10 min, 3 mL of 2M aq. Na<sub>2</sub>CO<sub>3</sub> was added followed by a solution of 4-methylphenylboronic acid (256 mg, 1.51 mmol) in 1.5 mL ethanol. The resulting mixture was stirred rapidly under reflux for 1 h. The mixture was cooled to room temperature and phases separated. After concentration, the residue was purified by chromatography (20% ether in hexane) to give 410 mg (96%) of 74.

**Methyl 2-[(*tert*-Butyldimethylsilyl)oxy]-4'-methylbiphenyl-2-carboxylate.** Compound 74 (406 mg, 1.22 mmol) was hydrogenated at 1 atm in 4 mL of methanol over 150 mg of 10% Pd/C to give 242 mg (1.0 mmol, 82%) of the 2-hydroxy compound. This was dissolved in 3 mL of CH<sub>2</sub>Cl<sub>2</sub>, and treated with 2,6-lutidine (174  $\mu$ L, 1.5 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (252  $\mu$ L, 1.1 mmol). The mixture was stirred 10 min, diluted with ether, washed with 1 M HCl, water, NaHCO<sub>3</sub>, and brine, dried (MgSO<sub>4</sub>), and concentrated. The product was chromatographed (5% ether in hexane) to give 315 mg (88%) of the title compound.

**Methyl 2-[(*tert*-butyldimethylsilyl)oxy]-4'-(bromomethyl)biphenyl-2-carboxylate.** The 4'-methyl compound (above) (312 mg, 0.87 mmol), *N*-bromosuccinimide (156 mg, 0.87 mmol), and AIBN (2 mg) were refluxed 3 h in of CCl<sub>4</sub>. The mixture was cooled to room temperature, filtered, and concentrated. The product was chromatographed (5% ether in hexane) to give 284 mg (75%) of the title compound. NMR analysis showed 3% CH<sub>3</sub> and 10% CHBr<sub>2</sub> impurities.

**Methyl 2-[N-Propyl-N-[[2'-(2-carbomethoxy-3'-(*tert*-butyldimethylsilyl)oxy)biphenyl-4-yl)methyl]amino]pyridine-3-carboxylate (75).** Compound 30 (R = H, R' = C<sub>6</sub>H<sub>5</sub>, R'' = CH<sub>3</sub>) (106 mg, 0.55 mmol) was alkylated with the above described bromomethyl compound (280 mg, 0.55 mmol) using the same method used when alkylating with 10. The product was purified by chromatography (30% EtOAc in hexane) to give 90 mg (30%) of 75.

**2-[N-Propyl-N-[[2'-(2-carboxy-3'-hydroxybiphenyl-4-yl)methyl]amino]pyridine-3-carboxylic Acid (76).** Compound 75 (40 mg, 0.1 mmol) in 0.5 mL of THF was treated with 0.2 mL (0.2 mmol) of a 1 M solution of tetrabutylammonium fluoride. The mixture was stirred 30 min, poured into brine, extracted with EtOAc, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to get 31 mg of the diester of 76. This was refluxed overnight in 1 N NaOH in water, methanol, and THF. After cooling, the mixture was acidified to pH = 2 with 1 N HCl to give 25 mg (86%) of 76.

**Radioligand Binding.** The binding of [<sup>125</sup>I]-Saralasin (NEN) to angiotensin II (type 1) receptors in rat liver was performed as described by S. J. Fluharty.<sup>29</sup> Rat liver membranes were prepared as described by D. M. Neville Jr.<sup>30</sup> and assayed using 1  $\mu$ M angiotensin to define nonspecific binding. The binding of [<sup>125</sup>I]-Tyr<sup>4</sup> angiotensin II (NEN) to type 2 receptors in bovine cerebellum was performed using a kit (NED-001) obtained from New England Nuclear.

Compounds were tested at multiple concentrations as required and analyzed as previously described.<sup>28</sup>

**pA<sub>2</sub> Determination in the Rabbit Aorta.** The method used was that of Chiu<sup>31</sup> with the exception in that aortic rings were used instead of spiral strips. The pA<sub>2</sub> calculation was done by the method of Schild.<sup>32</sup> For a full pA<sub>2</sub> determination, several doses of the drug was used and a Schild plot (log concentration of drug vs log EC<sub>50</sub> ratio-1) was made. The EC<sub>50</sub> ratio equals the EC<sub>50</sub> of angiotensin II with the drug, divided by the EC<sub>50</sub> of angiotensin II alone. For competitive antagonists, the slope of this plot should be between 0.90 and 1.15. For an estimated pA<sub>2</sub>, (sometimes known as pK<sub>i</sub>) the drug was tested at a single concentration of 10<sup>-7</sup> molar. Then, assuming the slope of the



Schild plot to be 1.00, the estimated  $pA_2 = \log(ED_{50} \text{ ratio} - 1)/10^{-7} = 7 + \log(ED_{50} \text{ ratio} - 1)$ .

**Oral Antihypertensive Activity in the Renal Artery Ligated Hypertensive Rat Model.** The conscious renal hypertensive rat model was used to evaluate the compounds. Male Sprague-Dawley rats (300–350 g) were used, and the method reported by Cangiano et al.<sup>30</sup> for renal artery ligation was employed to induce hypertension. Rats were used on the 6th or 7th day after renal artery ligation. Arterial blood pressure was measured from the indwelling femoral artery catheter. Data of blood pressure and heart rate were determined on line using a Buxco Cardiovascular Analyzer (Buxco Electronics Inc, Sharon, CT).

**Oral Antihypertensive Activity in the Furosemide Treated Spontaneously Hypertensive Rat.** Male SHR, 20–24 weeks old, were pretreated with furosemide, 10 mg/kg sc, at 22 and 4 h prior to the experiment. Measurements of arterial blood pressure and heart rate were similar to those described for the experiment with the renal artery ligated hypertensive rat.

**Pharmacokinetics.** The pharmacokinetic behavior of selected A-II antagonists was evaluated in male Sprague-Dawley-derived rats. The A-II antagonists were prepared as solutions in normal saline at concentrations appropriate to provide a 1 mL/kg volume for both intravenous and oral dosing. Each compound was administered as either a slow bolus intravenous dose in the jugular vein or as a oral dose (administered by gavage). Heparinized blood samples (~0.4 mL) were obtained from a tail vein of each rat at 0.1 (iv only), 0.25, 0.5, 1, 2, 4, 6, 9, 12, 15, and 24 h after dosing. The samples were analyzed by reverse-phase HPLC following liquid-liquid extraction from the plasma. Initial estimates of the pharmacokinetic parameters for NONLIN84<sup>33</sup> were obtained with the program CSTRIP.<sup>34</sup> Area under the curve (AUC) values were calculated by the trapezoidal rule over the time course of the study. The terminal-phase rate constant ( $\beta$ ) was used in the extrapolation of the AUC from 0 h to infinity (AUC 0– $\infty$ ). The total plasma clearance ( $CL_p$ ) was calculated by dividing the dose by the AUC. Assuming dose proportionality and correcting for the differences in dosing, a comparison of the AUC following oral dosing with that obtained following intravenous dosing provided an estimate of the bioavailability ( $F$ ).

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